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American Journal of Diseases of Children

Vol. 15 JANUARY, 1918 No. 1

STUDIES OF ACID PRODUCTION

I. THE VARYING SUSCEPTIBILITY OF CHILDREN TO ACIDOSIS. A PRELIMINARY REPORT *

MARGARET SAWYER, B.Sc., F. A. STEVENS, M.D.
AND
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Major and minor surgical operations on children are occasionally followed by an alarming increase in acid production, or acidosis, as it is commonly called. "Periodic vomiting of children," as well as many infectious diseases and disorders of the alimentary canal, is accompanied by an increased acid production. Even a casual survey of the literature leads to the impression that certain children are more susceptible to acidosis than others. The aim of the present work is to determine whether this individual susceptibility can be demonstrated experimentally.

METHODS

Apparently healthly male children between the ages of 4 and 8 years were placed in a metabolism ward under the supervision of a special nurse. The diets were prepared by a special dietitian. The urine at each voiding was separately collected in a jar and its approximate volume noted. It was preserved in a refrigerator after the addition of toluene. The next morning the twenty-four-hour volume was accurately measured and checked with the nurse's record. A creatin-free diet containing about 55 calories per kilogram was administered during the normal periods. Protein constituted 25, fat 30, and carbohydrate 45 per cent. of the total calory intake. The nitrogen intake was approximately constant throughout the normal and high fat periods. After the excretion of acid, ammonia and creatinin had become practically constant, the intake of each of the three classes of foodstuffs was reduced to one third. When distinct signs of acidosis appeared, the normal diet was resumed and continued until the excretion of acid and

* Submitted for publication Oct. 16, 1917.

* From the Departments of Home Economics and Internal Medicine, State University of Iowa.

ammonia had approximately attained their former level, when the fourth period was begun. During this period the protein intake remained the same as in the normal period, the carbohydrate was reduced to about 6 per cent., while fat rose to about 68 per cent. of the total calory intake. The normal diet was resumed when signs of acidosis appeared. The total nitrogen, ammonia, titratable acid,[1] creatinin[2] and creatin of the urine were quantitated each day. In a few instances the acetone bodies (acetone, aceto-acetic acid and oxybutyric acid in terms of acetone) and phosphates of the urine were estimated as well. Qualitative tests for acetone, sugar and albumin were carried out in routine fashion each day. The carbon dioxid combining power of the plasma was determined according to the method of Van Slyke[3] before breakfast, during the normal, low calory and high fat periods. In quite a few instances the acetone bodies, and in several, the calcium, glucose and fat content of the blood, were studied.

The acid equivalant of the food was computed from Sherman and Gettler's valuable tables.[4] The acetone bodies of the blood were determined according to Marriott,[5] glucose according to Lewis and Benedict,[6] calcium according to the micromethod of Marriott,[7] and fat according to the nephelometric method of Bloor.[8]

EXPERIMENTS

The present report includes observations on ten boys. The results are tabulated. Cases 5, 8 and 6, illustrating a severe, a moderate and a slight reaction, have been graphically represented (Charts 1, 2 and 3). In the tables the titratable acid and ammonia are expressed in terms of tenth-normal solution. According to Henderson and Palmer[1] these values are "strictly additive." The values for acetone and oxybutyric acid of the blood, which appear in the chart, are expressed in terms of milligrams per cent.

CASE 1.—C. C., aged 5 years; weighed 17 kg.; physical examination was negative, except for a discharging sinus from an old osteomyelitis.

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1. Henderson, L. J.: Jour. Biol. Chem., 1911, **9,** 403.
2. In the presence of acetone creatinin was determined according to the method of G. Graham and E. P. Poulton, Proc. Roy. Soc., Series B, 1913-1914, **87,** 205.
3. Van Slyke, Donald D.: Jour. Biol. Chem., 1917, **30,** 347.
4. Sherman, H. C., and Gettler, A. O.: Jour. Biol. Chem., 1912, **11,** 323.
5. Marriott, W. McK.: Jour. Biol. Chem., 1914, **18,** 507.
6. Myers, V. C., and Bailey, C. V.: Jour. Biol. Chem., 1916, **24,** 147.
7. Marriott, W. McK.: Private communication. We are indebted to Dr. Marriott for this courtesy.
8. Bloor, W. R.: Jour. Biol. Chem., 1914, **17,** 377.

TABLE 1.—DATA FROM CASE 1

Day	Titratable Acid, C.c.	Ammonia, C.c.	Creatinin, Mg.	Creatin, Mg.	Acetone Qualitative	Nitrogen in Urine, Gm.	P_2O_5 in Urine, Gm.	CO_2 Combining Power	Glucose in Blood, Mg., per Cent.	Acetone Bodies in Blood, Mg., per Cent.
1	—9*	226	211	51	....	9.1	0.85			
2	48	291	219	36	....	6.2	0.93			
3	94	338	223	37	....	9.8	1.48			
4	139	276	208	56	....	7.6	1.08			
5	86	270	218	57	....	8.0	1.0			
6	71	306	222	64	....	8.3	0.92			
7†	110	307	200	120	+	9.8	1.93	52	100	5.1
8†	161	622	196	102	+++	10.8	1.86			
9	70	778	198	97	++	9.6	1.12	21	50	30.0
10	36	446	222	13	+	6.6	0.46			
11	26	360	210	15	....	5.1	0.48			
12‡	54	192	194	32	+	6.5	0.82			
13‡	100	218	187	95	+	6.3	1.32	49	90	12.0
14	90	355	198	122	++	6.9	0.90			
15	41	365	230	7	....	6.8	0.52			
16	53	357	207	9	....	6.8	0.47			
17	43	316	200	22	....	6.6	0.63			

* Alkaline urine. † High fat diet. ‡ Low calory diet.

REMARKS: On the second day 300 c.c. of tenth-normal phosphoric acid solution (neutral red was employed as the indicator) was administered per os. This was followed by a prompt rise of the titratable acid and ammonia excretion, but by no subjective or objective symptoms. After twenty-four hours on the high fat diet the child complained of nausea. Some irregularity of the pulse was noted on the following day. Slight irregularity of the pulse was present after thirty-six hours on the low calory diet. The next morning the face was slightly flushed. During the period of high fat feeding the sinus discharged more freely than during the low calory period.

The response to the high fat diet was rapid and marked.

CASE 2.—C. G., aged 5 years; weighed 23 kg. Physical examination was negative.

TABLE 2.—DATA FROM CASE 2

Day	Titratable Acid, C.c.	Ammonia, C.c.	Creatinin, Mg.	Creatin, Mg.	Acetone, Qualitative	CO_2 Combining Power
1	125	385	276	192		
2	135	385	274	194		
3	120	395	274	174	.....	50
4*	140	330	272	178	+	
5*	170	500	256	236	++	
6*	240	815	244	290	+++	29
7	...	818	284	202		

* High fat diet.

REMARKS: The metabolism of this child (Case 2) was studied for another purpose and will be reported in detail in a subsequent paper. During the period of high fat feeding a slightly increased pulse rate and some restlessness were manifest.

CASE 3.—H. G., a nervous child with a neuropathic family history and marked chronic tonsillitis. The Wassermann reaction was one plus. The child was aged 8 years and weighed 17 kg.

TABLE 3.—DATA FROM CASE 3

Day	Titratable Acid, C.c.	Ammonia, C.c.	Creatinin, Mg.	Creatin, Mg.	Nitrogen in Urine, Gm.	Acetone in Blood, Mg., per Cent.	CO_2 Combining Power	Ca in Blood, Mg., per Cent.	Fat in Blood, Mg., per Cent.	Glucose in Blood, Mg., per Cent.
1	100	189	292	248	8.1					
2	81	225	264	341	8.5	0.4	51	13	670	50
3*	99	203	284	277	5.4					
4*	132	316	288	272	6.7					
5*	175	619	284	233	7.9	24.0	32	15	1,330	20
6	60	602	249	139	8.6					
7	30	393	250	95	7.5					
8	10	228	231	112	8.0					
9	10	189	271	181	9.6					
10	28	230	260	166	7.5					
11	13	328	284	231	9.8					
12†	112	227	271	176	10.1					
13†	96	476	260	238	11.2					
14	69	580	253	133	9.5	4.3	35	13	660	60
15	55	484	277	61	8.3					
16	65	283	249	48	7.2					
17	32	247	263	71	7.7					

* Low calory diet. † High fat diet.

REMARKS: The urine was collected in twelve-hour periods. The creatin output during the day was always considerably higher than at night. This is in agreement with the observation of Powis and Raper.[9] After the boy had been on the low calory diet for twenty-one hours he complained of nausea, and later, vomited. Nineteen hours later the pulse became intermittent and weaker. When the normal diet was resumed the child became comfortable in a remarkably short time.

After thirty-six hours on the high fat diet the patient became somewhat drowsy and the pulse became slower.

On the whole this child reacted very promptly. The low sugar value of the blood is significant.

Meat was fed during the first five days of the experiment.

This child responded to both diets fairly rapidly.

9. Powis, F., and Raper, H. S.: Biochem. Jour., 1916, **10,** 363.

CASE 4.—T. H., aged 6 years; weighed 18.3 kg. Physical examination was negative.

TABLE 4.—DATA FROM CASE 4

Day	Titratable Acid, C.c.	Ammonia, C.c.	Creatinin, Mg.	Creatin, Mg.	Nitrogen in Urine, Gm.	P_2O_5 in Urine, Gm.	Acetone Bodies in Blood, Mg., per Cent.	CO_2 Combining Power	Glucose in Blood, Mg., per Cent.
1	86	302	281	72	8.5	2.02			
2	120	240	264	61	8.3	1.29	3.2	67	78
3*	123	282	264	100	10.0	1.54			
4	133	530	253	113	11.5	1.75	19.0	35	86
5	62	449	271	24	9.4	0.90			
6	8	381	248	89	8.5	1.05			
7	50	297	251	72	9.0	1.26			
8	42	239	253	80	8.8	1.24			
9†	82	197	254	86	6.2	0.98			
10†	85	210	269	115	7.0	1.40			
11	99	361	233	124	9.8	1.42	22.0	31	74
12	22	384	234	21	8.6	1.02			
13	29	336	243	21	7.7	0.99			
14	56	302	254	33	8.1	1.03			
15	84	267	253	61	8.6	1.38			
16	80	276	239	39	8.9	1.88			

* High fat diet. † Low calory diet.

REMARKS: After twenty hours on the diet of high fat the patient reacted with vomiting; the pulse and respirations were slightly increased. During the experiment the patient had an acute rhinitis.

The response to the high fat diet was rapid in this case.

CASE 5.—C. H., aged 8 years; weighed 20.9 kg. Physical examination showed atrophy and paralysis of both legs following anterior poliomyelitis, chronic tonsillitis of medium grade, and adenoids. The child was also mentally deficient.

TABLE 5.—DATA FROM CASE 5*

Day	Titratable Acid, C.c.	Ammonia, C.c.	Creatinin, Mg.	Creatin, Mg.	Nitrogen in Urine, Gm.	P_2O_5 in Urine, Gm.	Acetone Bodies in Blood, Mg., per Cent.	CO_2 Combining Power	Glucose in Blood, Mg., per Cent.
1	45	281	182	67	6.5	1.22			
2	72	356	167	54	4.9	1.15			
3†	90	223	141	107	5.6	1.08	8.0	53	70
4†	160	579	160	200	7.4	1.37			
5	71	756	142	190	7.7	1.23	50.0	31	
6	47	663	159	64	5.3	0.49			
7	54	395	164	58	5.9	0.41			
8	56	346	172	136	7.5	0.52			
9	45	273	144	153	6.9	0.73			
10‡	87	242	146	173	8.0	1.27			
11‡	142	593	144	214	10.2	1.86	30.0	20	40
12	70	763	151	117	5.5				
13	30	632	152	44	6.6				
14	40	543	153	34	6.5				
15	52	443	157	52	6.4				
16	62	323	156	36	6.8				
17	90	320	156	73	6.6				
18	67	314	160	100	6.6				

* Refer to Chart 1. † Low calory diet. ‡ High fat diet.

REMARKS: On the low calory diet the boy's pulse became irregular in twelve hours and markedly so in thirty-six hours. At the end of forty hours emesis and dizziness were observed. Drowsiness set in at the end of forty-eight hours. After twelve hours on the high fat diet the face was slightly flushed. After twenty-four hours some vertigo was observed.

It was subsequently ascertained that this child developed a severe acidosis following the simple operation of section of the Achilles tendon.

The reaction to both diets was rapid and large.

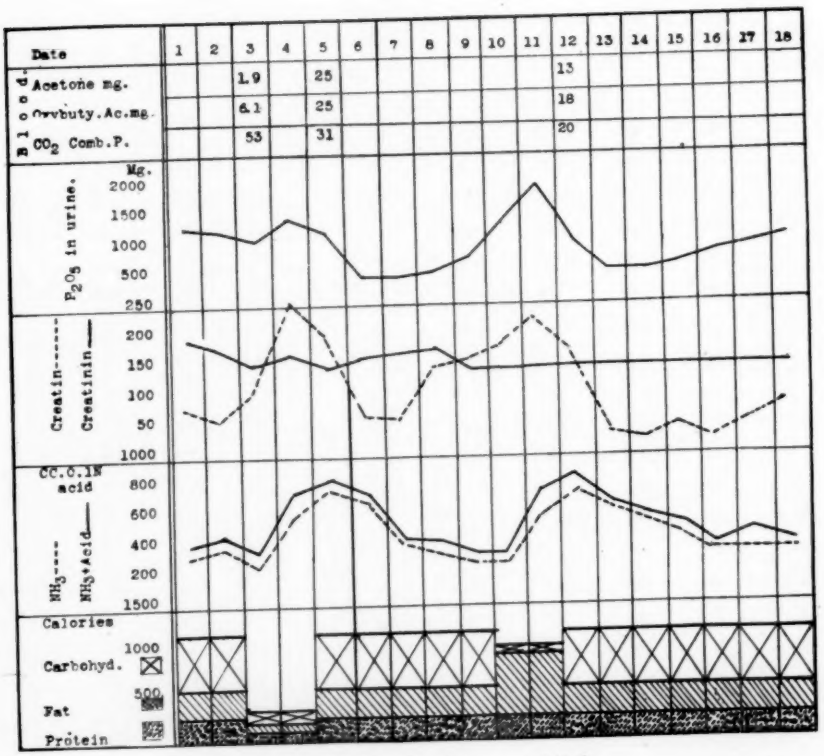

Chart 1.—Case 5. Severe acidosis.

CASE 6.—J. H., aged 5 years; weighed 20.5 kg. Physical examination showed enlarged tonsils filling half the lumen of the pharynx, and mental deficiency.

TABLE 6.—DATA FROM CASE 6*

Day	Titratable Acid, C.c.	Ammonia, C.c.	Creatinin, Mg.	Creatin, Mg.	Nitrogen in Urine, Gm.	Acetone Bodies in Blood, Mg., per Cent.	CO_2 Combining Power	Calcium in Serum, Mg., per Cent.	Glucose in Blood, Mg., per Cent.	Fat in Blood, Mg., per Cent.
1	88	376	336	184	9.2					
2	80	309	332	141	9.1					
3†	94	304	374	171	8.9	4.7	56	12	87	660
4†	119	270	332	278	8.3					
5†	112	227	316	306	7.6					
6†	86	329	282	261	7.2					
7†	87	266	273	226	6.0					
8†	75	312	216	201	6.4					
9†	62	284	285	191	5.0					
10	—15‡	275	293	196	8.2					
11	0	315	347	49	8.3	14.0	57	14	74	450
12	20	285	527	26	8.8					

* Refer to Chart 2. † Low calory diet. ‡ Urine was alkaline.

REMARKS: After forty hours on the low calory diet there was no evidence of acidosis except an irregular pulse, and no evidence of acidosis four days later. On the eleventh day the boy developed elevation of temperature (104 F.) coincident with a rise in the creatinin output. Later a typical measles rash developed.

This boy responded very little, if at all, after seven days on the low calory diet.

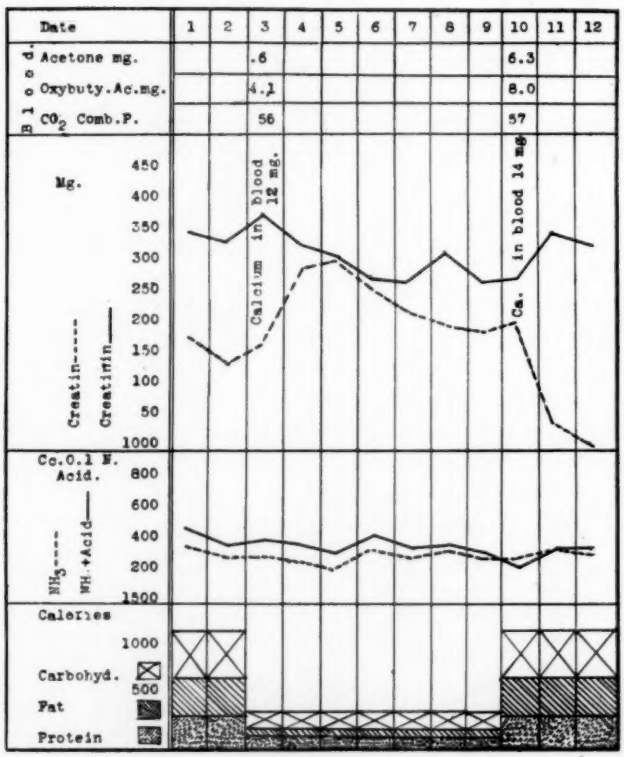

Chart 2.—Case 6. Little or no acidosis.

CASE 7.—T. K., aged 5 years; weighed 14.1 kg. Physical examination showed paralysis of both legs, due to anterior poliomyelitis, and slight cervical adenitis, but no evidence of the lymphatic state.

TABLE 7.—DATA FROM CASE 7

Day	Titratable Acid, C.c.	Ammonia, C.c.	Creatinin, Mg.	Creatin, Mg.	Nitrogen in Urine, Gm.	P_2O_5 in Urine, Gm.	Acetone Bodies in Urine, Mg.	Acetone Bodies in Blood, Mg., per Cent.	CO_2 Combining Power	Glucose in Blood, Mg., per Cent.
1	61	260	187	132	7.4					
2	59	239	190	108	7.9					
3	87	247	179	82	6.3	....	870	...	50	104
4	67	283	179	136	7.0	....	450			
5*	58	223	183	156	7.5	....	371			
6*	82	301	151	206	5.5	....	645			
7*	88	416	151	112	4.7	0.96	727			
8	46	347	157	83	6.6	0.70	191	27	41	54
9	15	254	164	26	5.6	0.77	112			
10	—10†	247	135	22	5.9	0.82	52			
11‡	58	212	155	47	7.0	....	68			
12‡	112	322	153	146	8.2	....	129			
13‡	110	543	144	159	8.4	1.16	588			
14	73	417	131	89	7.4	1.24	133	25	40	
15	32	322	130	47	7.9	0.93				
16	—31†	223	131	34	6.4	0.94				
17	0	227	142	39	6.7	1.06				

* Low calory diet. † Urine alkaline. ‡ High fat diet.

REMARKS: The combined sulphur and phosphorus content of the diet during the period of high fat feeding was equivalent to 400 c.c. of tenth-normal acid. During the period of low calory feeding no symptoms of acidosis were observed; during the period of high fat feeding slight drowsiness was noted, but no other symptoms.

The responses to the diet in this case were relatively slight.

CASE 8.—C. W., aged 8 years; weighed 22.2 kg. Physical examination showed paralysis of both legs due to anterior poliomyelitis and mild chronic tonsillitis.

TABLE 8.—DATA FROM CASE 8*

Day	Titratable Acid, C.c.	Ammonia, C.c.	Creatinin, Mg.	Creatin, Mg	Nitrogen in Urine, Gm.	Acetone Bodies in Blood, Mg., per Cent.	CO_2 Combining Power	Glucose in Blood, Mg., per Cent.	Fat in Blood, Mg., per Cent.	Calcium in Serum, Mg., per Cent.
1	31	291	300	235	7.9					
2	73	398	309	275	9.3					
3†	74	259	259	252	6.3	6.5	69	84	870	12
4†	120	212	278	375	6.8					
5†	130	278	270	261	6.6					
6†	130	432	276	192	5.8					
7†	86	437	286	146	5.1					
8	61	520	262	196	6.4	21.0	46	96	880	14
9	−15‡	306	276	123	6.8					
10	−15‡	240	274	196	7.9					
11	21	301	290	256	8.5					
12§	110	265	261	456	9.5					
13§	162	450	254	363	11.2					
14§	193	693	248	479	12.2					
15§	40	776	240	328	11.8	....	49	90	890	16
16	122	700	277	283	10.1					
17	14	493	270	227	9.1					
18	67	411	258	272	8.6					

* Refer to Chart 3. † Low calory diet. ‡ Alkaline urine. § High fat diet.

REMARKS: No symptoms were observed during the period of low calory diet. Sixty hours after beginning high fat diet the child complained of drowsiness.

Our impression is that the responses of this case to the diets were normal for a child of 8 years.

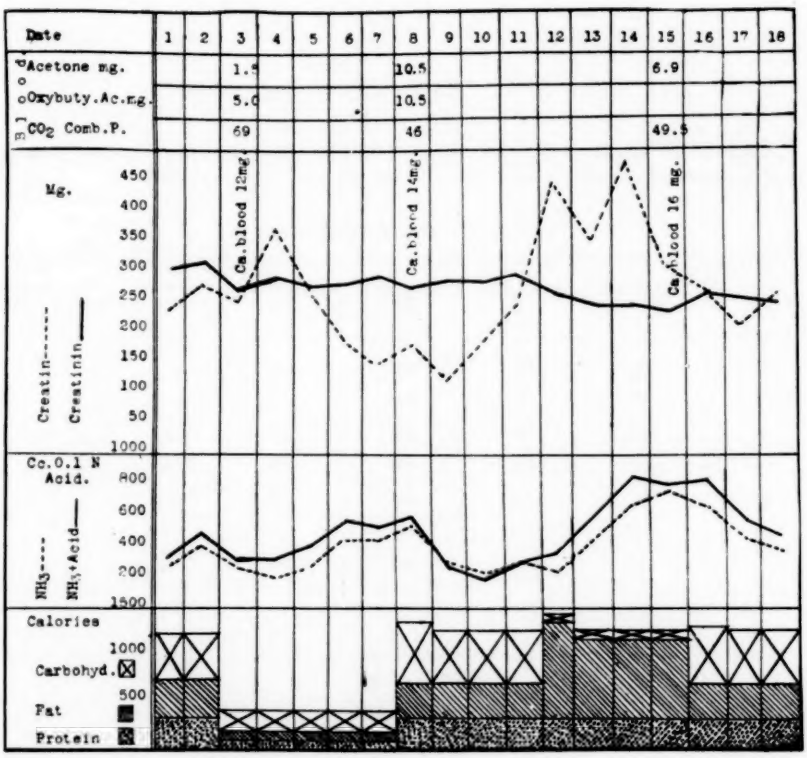

Chart 3.—Case 8. Moderate acidosis.

CASE 9.—R. W., aged 8 years; weighed 23.2 kg. Physical examination showed scar of mastoid operation, and that the tonsils had been removed.

TABLE 9.—DATA FROM CASE 9

Day	Titratable Acid, C.c.	Ammonia, C.c.	Creatinin, Mg.	Creatin, Mg.	Acetone, Qualitative	CO_2 Combining Power
1	100	465	332	96		
2	110	455	362	86		
3	100	465	336	143	.....	49
4*	120	390	362	124	+	
5*	120	425	342	216	++	
6*	145	580	334	250	+++	37
7	...	630	361	297		

* High fat diet.

Further studies carried out on Case 9 will be reported in a subsequent paper.

CASE 10.—B. W., aged 4 years; weighed 13.4 kg. Physical examination showed severe chronic tonsillitis with marked cervical adenitis, recent anterior poliomyelitis and a nervous temperament.

TABLE 10.—DATA FROM CASE 10

Day	Titratable Acid, C.c.	Ammonia, C.c.	Creatinin, Mg.	Creatin, Mg.	Nitrogen in Urine, Gm.	P_2O_5 in Urine, Gm.	Acetone Bodies in Urine, Mg.	Acetone Bodies in Blood, Mg., per Cent.	CO_2 Combining Power	Glucose in Blood, Mg., per Cent.
1	93	264	192	118	8.9	1.24				
2	86	223	218	147	7.5	1.32				
3	78	257	184	81	7.2	1.07	78			
4*	143	250	192	152	9.0	1.80	116	3.1	50	102
5	116	296	178	93	7.2	1.38	...	11.0	37	55
6	70	390	183	91	6.3	0.90				
7	37	218	169	36	6.8	0.97				
8	68	242	174	81	7.2	1.13	96			
9	55	219	185	68	7.6	1.18				
10†	89	169	182	116	5.8	1.13	215			
11†	92	199	171	139	5.5	1.23	446	16.0	39	66
12	47	337	156	121	7.1	0.74	120			
13	43	341	180	37	6.8	0.71	73			
14	57	297	156	54	6.0	0.71				
15	45	264	161	78	6.8	1.01				
16	54	255	173	67	6.9	1.03				

* High fat diet. † Low calory diet.

REMARKS: This child became restless and drowsy after twenty-four hours on the low calory diet. Twenty-four hours later the pulse became slow and irregular. Twenty hours after beginning the high fat diet vomiting occurred.

Although this child developed symptoms of acidosis very rapidly, the urine and blood analyses revealed only moderate changes.

TABLE 11.—SUMMARY OF DATA FROM PREVIOUSLY REPORTD CASES

Subject	Age, Years	Normal Period, Plasma Carbonate	Normal Period, Acetone Bodies* in Blood, Mg., per Cent.	Low Calory Period, Plasma Carbonate	Low Calory Period, Acetone Bodies* in Blood, Mg., per Cent.	High Fat Period, Plasma Carbonate	High Fat Period, Acetone Bodies* in Blood, Mg., per Cent.
T. H.	6	67	3.2	35 (2)	18.7	31 (1)	22
C. C.	5	52	5.1	48 (2)	12.2	21 (2)	30
T. K.	5	50	0.0	41 (3)	27	40 (2)	25
C. H.	8	53	8.0	31 (4)	50	20 (2)	30
H. G.	8	50	...	32 (3)	....	35 (2)	
J. H.	5	56	4.7	57 (7)	14		
C. W.	8	69	6.5	46 (5)	21	49 (4)	
B. W.	4	50	3.1	39 (2)	16	37 (1)	11
R. W.	6	51	...	.....	....	37 (1)	
C. G.	5	50	...	.....	....	29 (3)	
R. W.	8	49	...	.....	....	37 (3)	
L. S.	7	56	...	.....	...	30 (1)	
Average	...	54					

* Acetone bodies include acetone, aceto-acetic and oxybutyric acids (in terms of acetone). The numerals in parentheses refer to the number of days preceding the determination during which the child received the acid-producing diet.

DISCUSSION

A difference in reaction towards the acid-producing diets is apparent from the blood and urine analyses and also in the time which elapsed before a marked response occurred. The cause of this variation is at present more or less conjectural. Thus far we have not been in a position to associate it with a particular state or condition of the subject. All the children had been on similar hospital diets for months preceding this investigation. The response to the high fat diet was apparently more rapid and greater than to the low calory diet.

In a recent publication, Jeans and Johnston[10] observe that starvation does not always produce a marked increase of the acetone bodies in the blood of children. They refer to a patient who after a fast of five days showed 6.6 mg. per cent. of acetone bodies and 50.5 volume per cent. of plasma carbonate. At the end of eight days 22.6 mg. per cent. of acetone bodies and 56 volume per cent. of carbonates were present in the blood. This observation is quite similar to our own on Case 6 (Chart 1). On the other hand, we have found, in several instances,

10. Jeans, P. C., and Johnston, M. R.: AM. JOUR. DIS. CHILD., 1917, **14**, 57.

that noteworthy symptoms of acidosis may appear in less than twenty-four hours on the low calory diet. The symptoms most often encountered were nausea, vomiting, drowsiness, irregularity and slowness of the pulse and increase in the number of respirations.

The titratable acid of the urine, which is largely due to a preponderance of acid phosphate, increases as the result of change in the diet, before the ammonia.[11] This increase is accompanied by an absolute increase in the phosphate of the urine, without a compensatory decrease in the fecal output, as will be shown in a future publication.[12] The increased acid elimination is often followed by a period of diminished excretion and this is paralleled by the phosphate excretion.

The increase in the ammonia excretion becomes apparent, usually on the second day following the ingestion of the acid-producing diet and is prolonged for several days after the resumption of the normal diet. This observation is in agreement with that of Veeder and Johnston.[13]

Creatinin was practically constant throughout for each individual. As pointed out by Folin and others, it may be considered a constant and an indicator of the accuracy with which the urine has been collected. Creatin is uniformly increased during the periods of increased acid production. This increase is not attributable, apparently, to the acid condition per se[14] (Chart 2). The period of increase is often followed by one of markedly diminished excretion, occasionally lasting several days.

While the nitrogen excretion varied within rather wide limits, an unmistakable rise during the period of high fat feeding was present. This increase is uniformly accompanied by an increased creatin excretion and may be due to muscle breakdown. During the low calory period twice the amount of nitrogen ingested was eliminated through the urine. The increased elimination during the acid periods was occasionally followed by retention.

Qualitative tests for the presence of aceto-acetic acid in the urine were carried out daily by means of the Rothera modification of the Legal test. In some instances the urine of each voiding, following the administration of the acid-producing diets, was tested separately. We

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11. Sellards, A. W.: Bull. Johns Hopkins Hosp., 1912, **23,** 289.

12. Fitz, R., Alsberg, C. L., and Henderson, L. J.: Am. Jour. Physiol., 1907, **23,** 113. These authors found an increase of phosphorus in the urine of rabbits fed with hydrochloric acid. See also Steenbock, H., Nelson, V. E., and Hart, E. B.: Jour. Biol. Chem., 1914, **19,** 399.

13. Veeder, B. S., and Johnston, M. R.: Am. Jour. Dis. Child., 1917, **13,** 89.

14. The administration of hydrochloric or sulphuric acid to children may be followed by a rise in the excretion of ammonia and titratable acid in the urine without a rise in creatin (unpublished observations).

were occasionally surprised at the rapidity of the response. In two instances the high fat diet was instituted at 7:30 a. m. and a trace of aceto-acetic acid was found in the urine passed four hours later. Veeder and Johnston found that one-half of their patients (many of whom were infants), when deprived of nourishment, did not show an increase in the acetone bodies during the first twenty-four hours, but all responded during the second day of the fast. Their Case 16, however, responded very feebly with acetone and not at all with increased ammonia excretion.

Throughout these experiments we have obtained the impression that the carbonate values of the plasma are a reliable index of the severity of the acidosis. In one case (Case 6, Chart 2) we found an increase of the acetone bodies of the blood, with a normal carbonate value. While we have not determined the coefficient used by Fitz and Van Slyke,[15] the tables show that in a general way the combining power appears to be inversely proportional to the sum of the ammonia and titratable acid. The average normal plasma carbonate value for 12 children between the ages of 4 and 8 years was 54 volume per cent. (Table 11).

In a general way the increase of acetone bodies in the blood was proportionate to the severity of the acidosis. The glucose content of the blood was examined in eight cases; of these, six showed a decrease during the period of acidosis; two did not. Though this observation is suggestive, it should be confirmed on a larger series of cases. For want of blood we were unable to determine the calcium content of the serum in more than three cases. All showed an increase during the periods of increased acid production.

SUMMARY AND CONCLUSIONS

The reaction of ten children to acid-producing diets was studied.

Tables and charts recording the results of the blood and urine analyses have been made.

A careful survey of the tables and charts leads to the conclusion that the response to an acid-producing diet is a variable factor among the different children examined.

We desire to express our indebtedness to Prof. L. W. Dean for suggesting the problem and for his cooperation; to Prof. A. Steindler and Prof. A. H. Beifeld for their cooperation, and to Miss Helen Mougey for the care exercised in the preparation of the diets.

The research was made possible by a grant from the funds of the Graduate College of the State University of Iowa.

15. Fitz, R., and Van Slyke, D. D.: Jour. Biol. Chem., 1917, **30**, 389.

THE INTRAPERITONEAL INJECTION OF SALINE SOLUTION *

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The parenteral administration of water is a widely used therapeutic measure in the treatment of the severe nutritional disorders of infants, especially when, after continued vomiting and diarrhea, marked loss of body fluids has resulted. It is an efficacious means of combating this serious complication.

Without entering into a discussion as to the relative merits of the procedures used to introduce water, it may be said that the methods which have been employed leave much to be desired. The vomiting and diarrhea are usually so severe in the cases that require water that they prevent its administration by mouth or rectum. Intravenous injection is often difficult, and it is rarely possible to inject an amount sufficient for the purpose without throwing too great a burden on the circulation. The subcutaneous method is the one on which chief reliance has been placed. In our hands the results from this method have been disappointing. Absorption from the subcutaneous tissues is often very slow and after repeated injections is almost nil.

An efficient method for the administration of water for therapeutic purposes must fulfil several important requirements: (1) It must admit of the administration of comparatively large amounts at one time and permit of repetition at frequent intervals; (2) the water must be quickly absorbed; (3) the method must be simple of procedure, practicable and accompanied by a minimum of risk to the patient.

We believe that the injection of water[1] directly into the peritoneal cavity fulfils all of these requirements. This method is not original with us. We have employed it at the suggestion of Dr. Howland who saw it used as a routine measure on the service of Professor Garrod at St. Bartholomew's Hospital, London. No reference to this method has been found in the literature. It has been used extensively in the

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1. By water we mean physiologic sodium chlorid solution; the water is the essential element, and we believe that physiologic sodium chlorid solution is as effective as any of the other solutions which are recommended. It may be that as more information regarding the loss of salts in diarrheal conditions is obtained, a solution better meeting the requirements may be found.

Harriet Lane Home, The Johns Hopkins Hospital, for the past two years and with such satisfactory results that we consider it a distinct improvement on any of the other methods that we have used.

The amount of water that can be given depends on the size of the patient. In small infants 100 to 250 c.c. may be introduced and the injection can be repeated every twelve to twenty-four hours. In larger infants a greater amount (300 to 400 c.c.) may be given at one time. We have observed no untoward effects from the injection of such amounts, even when they have been frequently repeated.

The rapidity of the absorption of fluid from the peritoneal cavity is shown by the experiments of Dandy and Rowntree.[2] They found that 40 to 60 per cent. of phenolsulphonephthalein in solution was absorbed in one hour. The absorption took place directly into the blood stream and was not influenced by posture. Clinical evidence of its rapid absorption in patients we have treated is shown by the fact that the distention of the abdomen which usually follows the introduction of water intraperitoneally subsides after a short time. In a moribund patient 200 c.c. of normal saline solution were injected and the patient died six hours later. At the necropsy, which was performed immediately, less than 50 c.c. of the solution were recovered.

When this method is used great care in technic should be exercised. After considerable experience in the wards, however, controlling the method with animal experiments and with the findings at necropsy, we have become convinced that the attendant dangers are minimal. We have never seen any complications follow its use.

The following protocols are given to illustrate the effect of the injection of physiologic sodium chlorid solution into the peritoneal cavity of rabbits.

PROTOCOLS

ANIMAL 120.—Weight, 1,500 gm., injected with 50 c.c. physiologic sodium chlorid solution; killed three hours after injection. Necropsy findings: Hemorrhage (3 by 4 cm.) in the abdominal wall at site of injection, and slight edema of the subcutaneous tissues; injection of the vessels supplying this region. Point of entrance into peritoneum clean. Intestines show no abrasions. About 20 c.c. of slightly turbid fluid free in peritoneal cavity, with no large flakes of fibrin. Smears from fluid in peritoneal cavity showed a few polymorphonuclear cells, but no organisms. The cultures were sterile.

ANIMAL 117.—Weight, 1,600 gm.; injected with 50 c.c. normal saline solution, killed two and a half days after injection. Necropsy findings: Remains of slight hemorrhage in abdominal wall at site of injection. Point of entrance into peritoneal cavity not visible. Intestines everywhere smooth and glistening. No free fluid. No adhesions. Two or three flakes of fibrin found. Smears made from the flakes of fibrin show a few leukocytes, but no organisms. The cultures were sterile.

2. Dandy and Rowntree: Ann. Surg., 1914, **59**, 587.

The following is the report by Dr. A. H. Clark of the necropsy on a patient who was treated with intraperitoneal injections of physiologic sodium chlorid solution. The patient was a colored infant weighing 20 pounds, which was brought to the hospital with vomiting, diarrhea and acidosis and died thirty-six hours later. The infant received two intraperitoneal injections of physiologic sodium chlorid solution, one of 250 c.c. eighteen hours before death, and one of 200 c.c. six hours before death.

The abdomen is moderately distended and is symmetrical. At a point slightly below the umbilicus are two small fresh puncture wounds. On opening the peritoneal cavity the abdominal wall shows a slight extravasation of blood below these wounds, but there is no apparent abrasion of the peritoneal surface. Neither on the skin nor in the abdominal wall is there any evidence of an inflammatory reaction around these wounds. The peritoneal cavity contains about 20 c.c. of clear yellow fluid. The peritoneal surfaces are smooth and glistening and there are no localized areas of peritoneal roughening. The viscera are normally disposed and are not adherent. The intestines below the site of puncture show no abrasions.

The procedure must be carried out with strict aseptic precautions. It is not to be attempted where there is marked abdominal distention, at least not until this has been relieved, and care should be exercised that the bladder is not distended. Objection to the method may be raised because of the danger of puncturing the intestine during the introduction of the needle and from this same danger while the fluid is being introduced. This has not occurred in our series of cases.

TECHNIC

The technic is as follows: The patient lies in the recumbent posture with the movements of arms and legs restricted by a restraining jacket. The most favorable site for the introduction of the needle is through the linea alba just below the umbilicus. The skin is prepared after the usual surgical method, with iodin and alcohol, and the area may be rendered anesthetic with ethyl chlorid. The solution[3] is introduced by gravity from an infusion bottle. When the patient is restrained in the proper position and the site for the injection prepared, the skin and subcutaneous tissues are picked up between the thumb and the index finger and the needle,[4] pointing upward, is inserted at an oblique angle. After it has penetrated the peritoneum the fluid is allowed to flow into the peritoneal cavity.

The injection of the fluid is continued until the abdomen becomes slightly distended. It should not be introduced too rapidly or in too large quantities, to avoid the possibility of embarrassing the respiratory and circulatory systems. One hundred to 250 c.c. can be introduced in from fifteen to twenty minutes. The fluid flows in so rapidly that the solution does not become cooled below that of the body temperature. After the fluid has been introduced, the needle is withdrawn and the puncture wound covered with a sterile dressing. The

3. The solution which we have used is the so-called "normal saline solution" (0.8 per cent. sodium chlorid). This is made with freshly distilled water and promptly sterilized. It is injected at a temperature of 100 F.

4. We use an 18-gage nickeloid needle, 2 inches long, and the rubber tubing is fastened to the hub of the needle.

injection may be repeated after twelve to twenty-four hours, if necessary. The injection may be made, if desired, outside of the left rectus muscle about half way between the costal margin and the left anterior superior spine of the ileum.

The beneficial effects are first apparent in the general appearance of the patient. The feeble whine is often replaced by a strongr, more vigorous cry. The extreme restlessness lessens and thereafter the child frequently sleeps in a normal manner. The tongue, lips and the skin become moist, the fontanel is less depressed and the gray cyanosis or pallor disappears. The most striking change is the alteration in the facial expression. The eyes are less sunken and the anxious, painful expression is often lost. In a number of instances we have observed a very marked increase in the pulse rate and in the secretion of urine. The improvement is often so marked that only one injection has been necessary in patients who were in an apparently hopeless condition on admission. Occasionally a febrile reaction follows the introduction of the fluid. The temperature may range from 100 to 103 F., but it usually subsides after twelve to forty-eight hours. After the introduction of water the weight in some patients remains stationary, while in others there may be a gain in weight. After repeated injections there may be edema. A marked increase in weight is rarely permanent, but even with the loss of weight in such instances the improved general condition of the patient is maintained.

The results have been so encouraging that we have adopted this method in the treatment of all cases of severe gastro-intestinal disturbance when the introduction of water in sufficient quantity by mouth is impossible. If the condition of the patient demands it the intraperitoneal injection is made immediately on admission to the hospital. The indications for repeating the intraperitoneal injection are, the general condition of the patient and continuation of vomiting. When the vomiting has ceased water is given by mouth, and as early as possible thereafter the food which is indicated is begun. In patients with acidosis, alkaline therapy as recommended by Howland and Marriott[5] is used.

We do not wish to give the impression that the intraperitoneal route is to be used to the exclusion of the other prescribed methods for introducing water. Each serves its purpose. We do, however, recommend its use in cases in which the introduction of water as a therapeutic agent is urgently demanded.

While the case reports which are appended illustrate only the benefits resulting from the use of this method in the severe nutritional disturbances of infancy with and without acidosis, its usefulness may be extended to many other conditions in which the parenteral administration of water is indicated.

5. Howland and Marriott: Bull. Johns Hopkins Hosp., 1916, **27**, 63.

REPORT OF CASES

CASE 1.—M. H., aged 5 months; weight, 8 pounds.

The patient gained on woman's milk until 3½ months old, when it became necessary to feed her artificially. On a proprietary food the weight increased for a short time, then it became stationary, and finally, with the development of loose stools, fell rapidly. She was admitted to the hospital in a state of collapse, with gray color, sunken eyes, dry lips, weak cry, subnormal temperature and weak pulse. She vomited and had thirteen loose green stools in the first twenty-four hours in the hospital. There was no hyperpnea. The leukocytes were 30,000. The food was discontinued and only sips of water allowed by mouth. Three hundred c.c. of physiologic sodium chlorid solution were introduced into the peritoneal cavity at once. Following this, the temperature rose to 101 F. The pulse became stronger and the color better. The vomiting ceased and the patient was given water freely by mouth. The diarrhea continued and on the second day after admission the second intraperitoneal

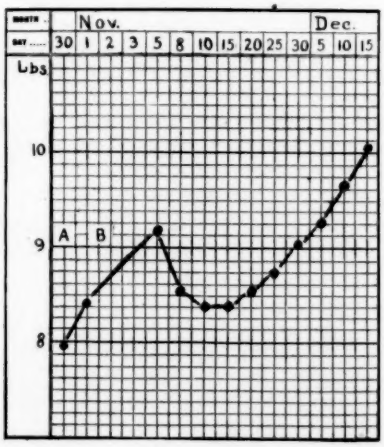

Chart 1.—(M. H., Case 1). Two intraperitoneal injections of physiologic sodium chlorid solution were given; at *A*, 300 c.c. and at *B*, 200 c.c. Note the weight curve.

injection of 200 c.c. of physiologic sodium chlorid solution was given. The child remained in a critical condition for several days, after which she began to improve and gained 2 pounds in six weeks.

CASE 2.—E. P., aged 5 months; weight, 10 pounds.

The patient, who had never been breast fed, was brought to the outpatient department because of vomiting and diarrhea. She did fairly well for seven days. Then there was a recurrence with a loss of 14 ounces in two days, and she was admitted to the ward. She presented the usual picture of an infant who had suffered from a severe and prolonged gastro-intestinal disturbance. There were the evidences of prostration—subnormal temperature, pallor and cold extremities—and of great loss of fluids (sunken eyes, pinched expression, dry and inelastic skin and anuria). She was drowsy, except when disturbed, and then she was restless and excitable. There was no hyperpnea. The heart's action was slow and weak. The abdomen was sunken. The temperature was 97 F. The leukocytes were 19,900.

Two hundred c.c. physiologic sodium chlorid solution were introduced into the peritoneal cavity at once. Fluid by mouth was withheld for twelve hours.

Then, as there had been no vomiting, protein milk was given at four-hour intervals and water every hour. There was a febrile reaction lasting twenty-four hours following the intraperitoneal injection. The response to the measures instituted was promptly shown by the improvement in the general condition of the patient. There was no further vomiting and the stools became normal after three days. The protein milk mixture was gradually replaced by a

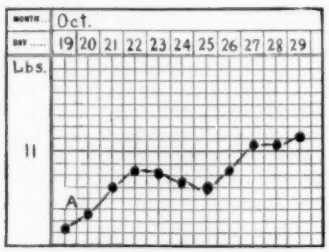

Chart 2.—(E. R., Case 2). Weight curve under treatment with one intraperitoneal injection of physiologic sodium chlorid solution at *A*.

whole milk mixture and the patient was discharged, having gained 14 ounces in ten days. Two weeks later, the infant was operated on for an acute mastoiditis, from which she made an uneventful recovery.

Case 3.—H. E., aged 7 weeks; weight, 6 pounds.

The patient was breast fed for two weeks, then received a cow's milk formula, and as she did not thrive, condensed milk was tried. During this time

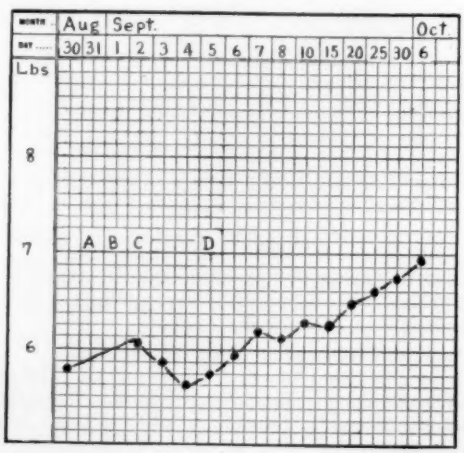

Chart 3.—(H. E., Case 3). Weight curve under intraperitoneal injections of physiologic sodium chlorid solution, 200 c.c. each at *A*, *B*, *C* and *D*.

vomiting occurred frequently and there was diarrhea. Four days before admission the vomiting and diarrhea became severe and she became rapidly worse.

When admitted to the wards the patient was cyanotic and the hands and the feet were cold. She was extremely restless and had a shrill, piercing cry. There was no hyperpnea. The temperature was 100 F. The leukocytes were 19,000.

The vomiting and diarrhea continued and her condition remained critical for four days. During this time the patient received three intraperitoneal injections of physiologic sodium chlorid solution (200 c.c., 200 c.c. and 150 c.c., respectively). After the third injection the condition of the patient was somewhat improved, she was less restless and the vomiting and diarrhea had subsided. On the seventh day the vomiting recurred and the stools again became loose and watery. The fourth intraperitoneal injection of 150 c.c. of physiologic sodium chlorid solution was given. There was no vomiting thereafter, the stools gradually became normal and she was discharged from the hospital having gained a pound in five weeks.

CASE 4.—G. H., aged 4 months; weight, 7 pounds 2½ ounces.

The patient did poorly after he was weaned at the third month. Condensed milk was given and he was admitted to the hospital because of vomiting which had persisted for two weeks.

He was an emaciated infant with a small amount of subcutaneous tissue. The eyes were sunken, the cry feeble and there were many petechiae on the abdomen. The heart's action was slow and weak; there was no hyperpnea. The temperature was 100 F. Leukocytes were 22,500.

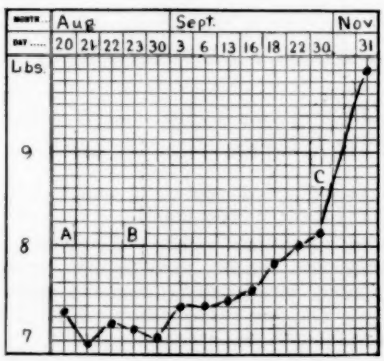

Chart 4.—(G. H., Case 4). Weight curve under intraperitoneal injections of physiologic sodium chlorid solution, 175 c.c. at *A* and 150 c.c. at *B*. *C*, weight two months later.

One hundred and seventy-five c.c. of physiologic sodium chlorid solution were introduced into the peritoneal cavity soon after admission and nothing was given by mouth because of vomiting. The infant's condition became much improved after the injection. There was no vomiting after the first twenty-four hours and he was given buttermilk. Two days after admission a second injection of physiologic sodium chlorid solution, 150 c.c., was given because of a collapse. After this the general condition remained good, although he did not gain. The buttermilk feedings were gradually replaced by breast milk. There was no vomiting and the stools became normal.

The patient was discharged six weeks after admission, having gained 12 ounces. He continued to improve and gained 1 pound and 14 ounces in the following month.

CASE 5.—G. S., aged 4 months; weight, 7 pounds.

The patient was breast fed for two months and then weaned. He did not gain in weight on a condensed milk mixture and when 2 months of age contracted pertussis. He vomited repeatedly after coughing, lost in weight, and for two weeks before admission had from six to eight loose, green, watery stools a day.

He was a very poorly nourished infant. The cry was feeble, there was a grayish pallor of the skin and the abdominal muscles were greatly relaxed. The

heart action was slow. The temperature was 97.5 F. The leukocytes were 18,500.

On admission to the hospital, 200 c.c. of physiologic sodium chlorid solution were injected into the peritoneal cavity. A most remarkable improvement was noted twelve hours later. His color was better, the cry stronger and the heart action more rapid. The stools became normal after three days and he was

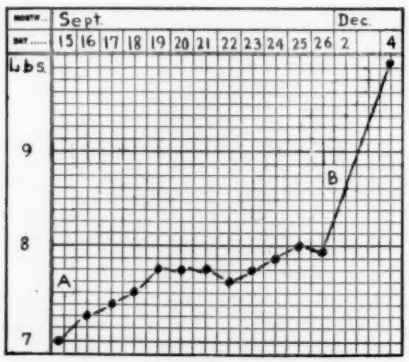

Chart 5.—(G. S., Case 5). Weight curve following treatment by intraperitoneal injection of physiologic sodium chlorid solution, 200 c.c. at *A*. *B*, weight two months after discharge.

discharged in eleven days, having gained 14 ounces. The improvement continued and he gained 2 pounds in two months.

CASE 6.—L. G., aged 5 months; weight, 11 pounds.

The patient was breast fed for two months, then received a cow's milk mixture. He progressed fairly satisfactorily, with the exception of an occasional mild attack of diarrhea. The day before admission he had several large watery stools and became very restless and irritable.

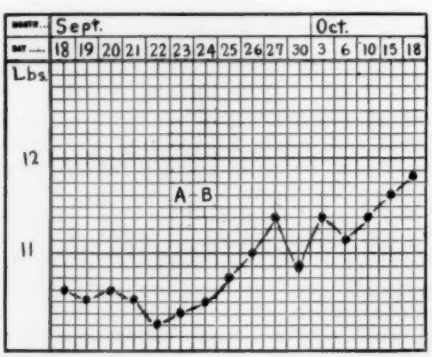

Chart 6.—(L. G., Case 6). Weight curve; 150 c.c. physiologic sodium chlorid solution given at *A* and *B*.

The infant was not thought to be particularly ill when admitted to the ward. There was no vomiting and the stools while loose were not very frequent (three to five per day). He was very irritable and restless. There was no hyperpnea. He was treated in the usual manner for five days. There was a loss of 6 ounces in weight and the stools did not improve. On the fifth day he suddenly became worse. There was cyanosis, irregular shallow breathing

and the heart action was rapid. Because of this collapse he was given 150 c.c. physiologic sodium chlorid solution into the peritoneal cavity. This was followed by general improvement in his condition. On the following day a second intraperitoneal injection (150 c.c.) was given. The improvement after the second injection was prompt; his general condition continued to become better and he was discharged at the end of one month, having gained 11 ounces in weight.

Case 7.—R. D., aged 2 months; weight, 7 pounds.

Because of failure to gain in weight the patient was weaned at 1 month of age and then received feedings of condensed milk. She did well for a time, but two days before admission developed diarrhea and vomiting.

On admission the child showed a moderate degree of malnutrition. The temperature was 101 F. The leukocytes were 12,300. An injection of 120 c.c. of physiologic sodium chlorid solution into the peritoneal cavity caused a marked improvement in the general condition, and alternate feedings of breast milk and buttermilk were begun. The temperature remained elevated and small amounts of the feedings were refused or regurgitated. The stools were loose.

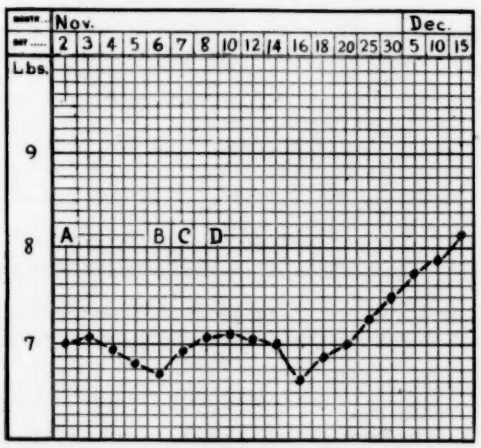

Chart 7.—(R. D., Case 7). Weight curve; intraperitoneal injections of physiologic sodium chlorid solution, 125 c.c. at *A*, 150 c.c. at *B*, 100 c.c. at *C* and 175 c.c. at *D*.

The fourth day after admission, the infant became much worse and hyperpnea was observed. This suggested an acidosis, which was verified by the laboratory tests. The carbon dioxid tension of the alveolar air was 24 mm. The RpH[6] of the blood serum was 7.8. Seventy c.c. of a 4 per cent. solution of sodium bicarbonate were injected into the longitudinal sinus at once; sodium bicarbonate was also given by mouth. One hundred and fifty c.c. of physiologic sodium chlorid solution were injected intraperitoneally and after sixteen hours 100 c.c. were given again. A third injection of 175 c.c. of the saline solution was given in the following twenty-four hours. After the administration of a total of 15 gm. of sodium bicarbonate in twenty-two hours, the carbon dioxid tension in the alveolar air was 38 mm. and the RpH of the blood serum was 8.3.

There was a marked improvement in the patient's condition after the administration of water and of alkali, but she remained in a critical condition for

6. Marriott: Arch. Int. Med., 1916, **17,** Part 1, p. 840.

about eight days. After this she began to improve and was discharged after six weeks, having gained 1 pound 2 ounces.

CASE 8.—J. E. W., aged 2½ months; weight, 4 pounds 14 ounces.

The patient did not thrive on woman's milk and was weaned at 1 month of age. He developed diarrhea on cow's milk and was brought to the hospital with convulsive twitchings, cyanosis, short gasping respirations, a subnormal temperature and weak pulse. The leukocytes were 26,800. He had eight loose stools during the first twenty-four hours in the hospital. He was given three intraperitoneal injections of salt solution (of 100, 100 and 160 c.c., respectively) on successive days. He remained in a critical condition for three days. There-

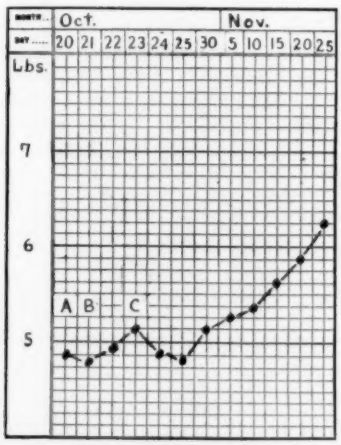

Chart 8.—(J. E. W., Case 8). Weight curve; intraperitoneal injections of physiologic sodium chlorid solution, 100 c.c. at *A* and *B* and 160 c.c. at *C*.

after he began to improve and was discharged from the hospital having gained 1½ pounds in five weeks.

CASE 9.—H. S. (15101), aged 6 months; weight, 11½ pounds.

The baby was breast fed for five months and then received a condensed milk formula. She lost in weight, vomited and had diarrhea on this food, and was brought to the hospital because the vomiting and diarrhea became worse. The patient was admitted to the wards in a critical condition. She was very poorly nourished and very restless. Hyperpnea was present. The laboratory tests showed that there was an acidosis. Blood serum; Ph 7.3; RpH 7.7. The temperature was 104 F. There was constant vomiting and there were seven large and watery stools in twenty-four hours. Treatment was begun at once. All food by mouth was discontinued; 200 c.c. physiologic sodium chlorid solution were injected intraperitoneally, and 75 c.c. of a 4 per cent. solution of sodium bicarbonate were injected intravenously. The child's general condition improved promptly and the respirations became normal in character. A second intraperitoneal injection of the saline solution was given on the following day and sodium bicarbonate was also administered by mouth. The vomiting ceased and on protein milk the stools improved. The temperature gradually became normal and the patient was discharged ten days after admission.

PROGRESS IN PEDIATRICS

REVIEW OF THE COMMUNICABLE DISEASES*

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THE COMMUNICABLE DISEASES

Epidemiology. — Kelley,[1] believing that the milk supply is often implicated as the channel of infection in epidemics of communicable diseases, when, as a matter of fact, it is the exception to find that any attempt has been made to determine the probable source of infection, tabulated the investigations of the Massachusetts State Board of Health field force, covering outbreaks and epidemics over a period of five years. His analysis does not corroborate the statements recently made in the literature, the experience in Massachusetts indicating that even in raw milk the transmission of diphtheria is so rare as to be negligible, and that the transmission of scarlet fever, though commoner, is of very small percentage significance.

Control.—Josephine Baker[2] tells us that in New York City the chief reliance for the prevention of the spread of the communicable diseases is placed on the system of school medical inspection. Children are excluded on suspicion; pupils in rooms where contagious diseases have occurred are inspected daily; cultures are taken from all suspected cases; the school doctor inspects daily all children suspected of being ill and all who have returned to school after an illness or unexplained absence. All absentees of more than three days' duration are visited at home. The wisdom of keeping children in school in the presence of communicable diseases is emphasized. Systematic observation offers a greater degree of protection to other children than can be attained by allowing them to mix indiscriminately on the street when the schools are closed. The same writer[3] makes further suggestions for the control of these diseases: (1) a broad campaign of public health education, as without the cooperation of the public not much can be accomplished; (2) the keeping of a home record concerning school progress, the occurrence of communicable diseases and the physical welfare of

* Submitted for publication Oct. 15, 1917.

1. Kelley: Jour. Am. Med. Assn., 1916, **67,** 1997.
2. Baker: Am. J. Pub. Health, 1916, **6,** 1078.
3. Baker: New York Med. Jour., 1917, **105,** 1198.

the child; (3) the general use of the Schick test and the immunization of all susceptible children by means of toxin-antitoxin injections; (4) the exclusion from school of all children with a bronchial cold, together with the establishment of whooping cough clinics; (5) more detailed attention to personal hygiene and to the hygiene of the nose and throat.

Hospitalization.—Wilson[4] says that public sentiment generally is opposed to admitting most cases of a communicable nature to special hospitals, but he advocates giving health authorities the power to order to the hospital cases of communicable disease in every instance in which there is failure to comply with the health laws, and every community should have hospital accommodations sufficient to care for all nonquarantinable cases of this nature. With this control, Wilson is confident that there would never be an epidemic in the accepted definition of the term.

Caverly[5] calls attention to the fact that house quarantine is at best cumbersome, unscientific and often ineffective, and favors the establishment of isolation hospitals or wards connected with general hospitals, especially in rural communities, the latter combining, by towns or counties, in their support.

Quarantine and Disinfection.—Hubbard[6] sent a questionnaire to sixteen of the largest municipalities regarding the procedure in the case of the communicable diseases. He found that some cities are ultraconservative, and concludes that while no one knows the best, safest and most economical method of prevention and control of these diseases, it should be appreciated that the most desirable system will be that which is freest from unnecessary restraint and at the same time is consistent with demonstrated methods and scientific knowledge. Williams[7] questioned eighteen prominent physicians regarding the minor communicable diseases, and decides that all three should be reported if any attempt is to be made to control and abolish them; chickenpox, because it is sometimes confused with smallpox, and because it may be a serious disease itself; German measles, because of its frequent confusion with scarlet fever; and mumps, because it may be more serious than commonly supposed.

Laubach[8] found that pathogenic bacteria can seldom be isolated from books handled by the sick and, consequently, there is no reason for believing that they may serve as vehicles of infection, although the

4. Wilson: Am. Jour. Pub. Health, 1916, **6,** 261.
5. Caverly: Am. Jour. Pub. Health, 1916, **6,** 1196.
6. Hubbard: Jour Am. Med. Assn., 1915, **65,** 1781.
7. Williams: Albany Med. Ann., 1916, **37,** 343.
8. Laubach: Bull. Johns Hopkins Hosp., 1916, **27,** 183.

fact that pathogenic bacteria can be recovered from artificially infected books after a long period of time, is sufficient reason for disinfection of the latter. Knause[9] holds that mediary disinfection is a most important factor in the control of communicable diseases, and thinks it is neglected by both the attending physician and the health authorities. Terminal disinfection by cleaning and renovation is desirable from a sanitary and a psychological point of view, but fumigation is costly, and as a factor in the control of these diseases it is of negative value. Walcott[10] thinks that a safe working rule is to scrub with soap and water as high as a man can reach the room in which a patient has been ill. When fumigation is discontinued, a good many dollars will be released to be spent to better advantage.

Aseptic Nursing. — Richardson[11] of Providence reports on the occurrence of cross infections among 4,689 patients suffering from communicable diseases, cared for during the period March 1, 1910, to Jan. 1, 1916, using aseptic nursing technic. The percentage of cross infections was 3.5. Richardson concludes that it is fair to state that air infection is a rare occurrence and that rigid asepsis is of primary importance. Hospitals for communicable diseases should not have wards of over six to ten beds each, and should be provided with a sufficient number of smaller units to accommodate all new patients for an observation period.

Cowie[12] recites his experience with 223 cases in the communicable disease division, using the aseptic technic method as practiced in Providence. Only five instances of cross infection occurred, apparently the result of faulty technic on the part of one nurse. His objections to the method are the danger from incubating cases and from diphtheria carriers among the nurses and attendants. Actual experience, however, has tended to minimize in his mind the probable danger from either of these sources. Miss Burby[13] reports only one cross infection in two years, in the communicable disease wards of the New London Memorial Hospital, while two nurses contracted diphtheria. Aseptic technic is practiced, each room being equipped with running water and each nurse being required to wash her hands after doing or touching anything in the line of duty, no matter how trivial.

Wilson[14] agrees that communicable diseases can be treated in general hospitals and that other patients can be guarded against infection.

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9. Knause: Am. Jour. Pub. Health, 1916, **6**, 364.
10. Walcott: Boston Med. and Surg. Jour., 1916, **174**, 337.
11. Richardson: Am. Jour. Pub. Health, 1916, **6**, 995.
12. Cowie: Jour. Mich. Med. Soc., 1916, **15**, 240.
13. Burby: Mod. Hosp., 1916, **7**, 306.
14. Wilson: Mod. Hosp., 1916, **7**, 316.

Thomson[15] has kept very careful track of 497 patients suffering from 657 communicable diseases that were treated in a twelve-bed ward over a period of some three and a half years. He concludes that scarlet fever, diphtheria, rubella and mumps are not air borne; that whooping cough may be; and that chickenpox is air borne early in the disease.

Incubation Period.—On the basis of the work done by Bull,[16] it is suggested[17] that the incubation period of the communicable diseases is due to the fact that the infecting agents must become adapted to the adverse conditions encountered in the newly infected host before they can multiply sufficiently to produce symptoms of disease. It is further suggested that epidemics may arise because the infectious agent is passed from person to person in the ascending stage of the disease, and thus enters new hosts in a state of maximum resistance to the natural antibodies of such individuals. When early contacts are avoided, epidemics tend to subside because the infectious agent is weakened by the action of acquired antibodies during convalescence.

Death Rate.—Studying the death rate from the acute infections, Graham[18] found that among infants less than 1 year old, whooping cough caused more deaths than measles, diphtheria or scarlet fever. Measles showed the next highest mortality, then diphtheria, and lastly, scarlet fever. During the second year, diphtheria caused more deaths than either of the others, while more deaths occurred from measles during the second year than at any other period. From the second to the fifth year diphtheria is the most serious, scarlet fever is next, measles is a close third, and whooping cough is not far behind. From the second to the tenth year the diphtheria mortality is higher than that of all other acute infections combined.

Royer[19] presents statistics to show that public health control has been responsible in part for the decline in the measles death rate from a yearly average of 1,300 to approximately 700; that there has also been some decline in the diphtheria death rate and in that from whooping cough. How much of the latter depends on public health activities is doubtful, while Royer feels that scarlet fever has not shown the same tendencies to yield results from public health control.

Kelley[20] believes that the achievements of preventive medicine during the past twenty years have been striking, especially in reducing the mortality rate from diphtheria and certain other infections, but it is

15. Thomson: Lancet, London, 1916, **1,** 341.
16. Bull: Jour. Exper. Med., 1916, **24,** 7.
17. Editorial: Jour. Am. Med. Assn., 1916, **67,** 1305.
18. Graham: Jour. Am. Med. Assn., 1916, **67,** 1272.
19. Royer: Penn. Med. Jour., 1916, **19,** 432.
20. Kelley: Boston Med. and Surg. Jour., 1915, **173,** 163.

not so good in scarlet fever, measles and whooping cough. To further reduce the prevalence of the communicable diseases the following means must be loked to: (1) better education of the public as to the real nature of communicable disease transmission; (2) more efficient diagnoses; (3) prompt reporting to the authorities; (4) efficient isolation.

While the death rate as a whole, and for certain diseases, shows a decrease in the past year (1916), that for measles and whooping cough, according to Veeder,[21] remains practically the same, between 9,000 and 10,000 deaths occurring annually in the United States from those diseases. Somewhere between 5 and 10 per cent. of the mortality of the first year of life which may be lessened, is due to measles and whooping cough.

Treatment.—Goodridge,[22] reviewing the subject of circulatory failure in the acute infections, concludes that there is neither clinical nor experimental evidence in support of the belief that failure of the vasomotor center is the cause of the symptoms of circulatory failure which occurs in these diseases. He finds alcohol and strychnin absolutely worthless in the treatment of circulatory failure. Epinephrin and pituitary extract are useful in sudden circulatory collapse, but their action is not a sustained one.

Lemoine and Devin[23] used Milne's[24] method of prophylaxis in the treatment of measles, scarlet fever, mumps and diphtheria, without the development of any cross infections or complications. They believe that when the method is painstakingly applied, the period of isolation after the communicable diseases can be materially shortened. Other French clinicians[25] report excellent results with the same method, chiefly in scarlet fever.[26]

GERMAN MEASLES

Few articles have appeared during the past two years on the subject of rubella, and these have been chiefly clinical reports.

Comby,[27] from his observations on 132 cases, believes the disease to be an eruptive fever, distinct from measles and scarlet fever. The scarlatiniform variety of rubella is not a distinct affection, as claimed by Duke,[28] but only a form of German measles.

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21. Veeder: Arch. Pediat., 1917, **34,** 321.
22. Goodridge: Am. Jour. Med. Sc., 1917, **153,** 107.
23. Lemoine and Devin: Bull. de l'Acad. de méd., 1916, **75,** 385.
24. Milne: Lancet, London, 1911, **1,** 1070.
25. Vevey: Bull. gén. de thérap., 1915-1916, **168,** 831.
26. Chantemesse: Bull. de l'Acad. de méd., 1915, **74,** 681.
27. Comby: Arch. de méd. d. enf., 1916, **18,** 293.
28. Duke: Lancet, London, 1900, **2,** 89.

Gray[29] reports 283 cases, one third of which had had a previous attack. Six cases ended fatally, a mortality of 2.1 per cent. Box[30] analyzes 850 cases and finds that previous attacks undoubtedly occurred in twenty-six of these. All observers agree that the incubation period is long, between twelve and twenty days. Lewis[31] believes that "German measles" is not a diagnosis, and as such is unnecessary in medical nomenclature. He thinks that so-called German measles is either true scarlet fever, measles or true grippe.

Adamson[32] reports two cases of the so-called fourth disease of Duke,[28] both with two relapses each.

Greeley[33] has continued his work with the diplococcus-like organism which he found to be constantly present in varicella vesicles, and has been able to cultivate the organism on artificial mediums. He has conducted agglutination and complement fixation tests, but does not find that specific value can be attached to agglutination tests, the varicella antigen giving negative results with the corresponding serums and positive tests with most normal serums tried.

Kolmer[34] showed that an antibody in the nature of an amboceptor is present in the serum of persons suffering with varicella, and will absorb complement in the presence of an antigen prepared from the cutaneous lesions of the disease. The percentage of positive reactions, and particularly the degree of complement fixation, is small, however.

Experimenting with protective chickenpox vaccination after the manner of Kling,[35] Sophie Rabinoff[36] found the chief difficulty in obtaining the virus. Animal experimentation thus far has been unsuccessful, and it is necessary to use material directly from either the vesicles or pustules from an active case of the disease. Among 142 susceptible children, 114, or about 75 per cent., developed varicella, while in a group of 76 vaccinated children, only 6, or about 8 per cent., contracted the disease, all of them, however, within the incubation period, which was about sixteen days. The duration of the protection could not be determined.

Thomson[15] is convinced that chickenpox is air borne early in the disease, it rarely being carried in the air as late as the third day, but apparently not afterward. Thomson exposed susceptibles suffering from scarlet fever to cases of scarlet fever and chickenpox. The last

29. Gray: New York Med. Jour., 1915, **94,** 104.
30. Box: Practitioner, 1917, **98,** 501.
31. Lewis: Boston Med. and Surg. Jour., 1917, **176,** 742.
32. Adamson: Lancet, London, 1916, **1,** 290.
33. Greeley: Med. Rec., New York, 1916, **90,** 265.
34. Kolmer: Jour. Immunol., 1916, **1,** 59.
35. Kling: Berl. klin. Wchnschr., 1913, **50,** 2083.
36. Rabinoff: Am. Jour. Obst., 1915, **72,** 526.

case was introduced as early as the eighth day of the chickenpox, and yet no infection resulted, but it has not been determined just how early the chickenpox patient ceases to be a danger to those with whom he comes in contact. Enough has been accomplished to show that it is needless to keep varicella patients separate from others as long as it has been generally supposed necessary.

Several clinical cases are reported. Wyler[37] tells of a corneal ulcer complicating chickenpox, which he believes to be the eruption of a pock. Smith[38] observed a case which showed symptoms indicating unmistakably the existence of a lesion in the cord, an acute myelitis. Campbell[39] reports a hemorrhagic chickenpox in an infant 5½ months old, with death twenty-seven hours after the onset of the hemorrhages. Guidi[40] saw a case of varicella with localization in the larynx, necessitating intubation.

MUMPS

From experiments conducted on cats, Wollstein[41] deduces that the salivary secretion in mumps contains a filterable substance capable of setting up a series of definite pathologic changes when inoculated into the testicle and parotid glands of that animal. Whether this active material contains a micro-organism, and if it does, whether it is the specific microbic cause of mumps, remains to be seen.

Feiling[42] presents a critical review of the entire subject of mumps, with a table of forty-one examinations of the blood. Twenty-one of these patients had a white count somewhere between 6,000 and 10,000, the highest 15,600; the rest were below 6,000, the lowest being 4,600. In every case there was a lymphocytosis, either relative or absolute.

Marcovici[43] examined the blood of ten cases of uncomplicated mumps, first on the second or third day, and again on the tenth. In the early stages the count was normal, ranging from 5,900 to 7,150, the mononuclears being increased at the expense of the neutrophils, and the eosinophils being normal or entirely absent. In the second stage there is a leukocytosis of the neutrophilic type, ranging from 10,000 to 20,000, with an increase of the eosinophils to 7 per cent.

The most interesting work on mumps, however, is that of Hess,[44] who attempted to confer immunity to the disease by the use of blood from convalescent patients. He inoculated twenty children who had

37. Wyler: Jour. Am. Med. Assn., 1917, **68,** 1476.
38. Smith: Am. Jour. Dis. Child., 1915, **10,** 445.
39. Campbell: Canada Med. Assn. Jour., 1915, **5,** 610.
40. Guidi: Riv. di clin. pediat., 1915, **13,** 435.
41. Wollstein: Jour. Exper. Med., 1916, **23,** 353.
42. Feiling: Quart. Jour. Med., 1915, **8,** 255.
43. Marcovivi: Folia hematol., 1915, **20,** 136.
44. Hess: Am. Jour. Obst., 1915, **72,** 183.

never had mumps with the blood of convalescents, using 6 or 8 c.c. from the vein in the elbow and injecting it intramuscularly. Four of these children were inoculated from patients who had just recovered and in whom there was still some parotid swelling. A second group were inoculated from patients about ten days recovered, while the third group received blood from children who had had the disease several years previously. All the children were put into mump wards, but not one of the inoculated children contracted the disease, while in one ward eleven susceptible children contracted the infection. The blood from old cases seemed to be just as efficacious as that from recently recovered patients.

Case Reports.—Lavergne[45] saw symptoms of meningitis precede those of mumps, and this suggested the possibility that certain conditions described as "meningeal states" may have been parotid meningitis, with which the inflammation of the parotid glands was too slight to attract attention. Josephson[46] encountered a suppurative process in the right adnexa secondary to an attack of mumps, and believes that this demonstrates that the latter disease is a general infection which is liable to attack any of the glands. As a rule, the testicles bear the brunt of the attack, secondary to the parotids, the ovaries and the mammary glands coming next in frequency. Chillingworth[47] reports a case which apparently affected the pancreas first, then the left ovary, then the right ovary and finally both parotids simultaneously.

Voisin[48] saw a fatal case of meningitis complicating mumps; Batigne[49] reports a case of orchitis as a complication; Sainton and Bosquet[50] tell of a case of typical mumps complicated by cerebrospinal meningitis, the latter verified bacteriologically; Sainton and Huriez[51] observed a rare complication of mumps, a double paralysis of the brachial plexus; Massary and Tockmann[52] analyzed a series of 243 cases of mumps, of which fifty-nine, or 24 per cent., developed orchitis, and fifty-six, or 23 per cent., developed a meningeal reaction; Eichhorst[53] reports two cases of mumps in which bradycardia was especially striking. He believes the condition to be due to a toxin.

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45. Lavergne: Arch. de méd. d. enf., 1917, **20,** 182.
46. Josephson: Upsala Läkaref. Förh., 1915-1916, **21,** 523.
47. Chillingworth: Brit. Med. Jour., 1916, **1,** 653.
48. Voisin: Bull. et mém. Soc. méd. d. hôp. de Paris, 1916, **40,** 223.
49. Batigne: Ann. d. mal. ven., 1916, **11,** 340.
50. Sainton and Bosquet: Bull. de l'Acad. de méd., Paris, 1915, **74,** 368.
51. Sainton and Huriez: Bull. et mém. Soc. med. d. hôp. de Paris, 1915, **39,** 809.
52. Massary and Tockmann: Bull. et mém. Soc. méd. d. hôp. de Paris, 1916, **40,** 1035.
53. Eichhorst: Med. Klin., 1915, **11,** 535.

Bertelsen[54] relates his experience with mumps which was brought to Greenland in 1913. Of the 2,425 individuals in the district, about 1,500 contracted the disease. No infant under 2 years of age was affected.

WHOOPING COUGH

Epidemiology and Prophylaxis.—The best hope for good results in the control of whooping cough, according to Crum,[55] lies along educational lines, physicians, teachers, nurses, parents and older children all needing information as to how the presence of the disease may be detected and what to do when it is discovered. Intensive statistical study of the disease is necessary, and if properly conducted would go far to remove the present widespread ignorance of the disease, the gravity of which is not appreciated either by the general physician or the public.

In Morse's[56] opinion the greatest obstacles to the control of the disease are the facts that the early symptoms are so indefinite that it is most contagious at the time when it is impossible to recognize it clinically, and that extremely mild types are common. It is evident that while examination of the blood and sputum and the complement fixation test are of undoubted value in the diagnosis of whooping cough, they are not at present of great practical utility in the recognition and prevention of the spread of the disease. Isolation of the sick, especially from babies and young children, should be insisted on, and if this is impossible, the cases should be sent to hospitals constructed on the "shack" plan, in order to give the children the maximum amount of fresh air. Morse does not believe that isolation should be maintained beyond the fifth or sixth week.

Abt[57] urges that all concerned in the prevention of disease cooperate to enforce such regulations as will prevent those sick with whooping cough from attending school, visiting playgrounds and using public conveyances, and in isolating those sick or suspected of being sick with the disease.

Tissier[58] reports that in a recent epidemic the adult more often transmitted the disease to the child than vice versa, which is contrary to what is usually the case.

Pathology.—Rhea[59] describes the lesions present in the trachea and bronchi of dogs ill with distemper, and calls attention to the similarity

54. Bertelsen: Ugesk. f. Laeger., 1915, **77,** 1925.
55. Crum: Am. Jour. Pub. Health, 1915, **5,** 994.
56. Morse: Boston Med. and Surg. Jour., 1916, **175,** 723.
57. Abt: Jour. Am. Med. Assn., 1916, **67,** 1787.
58. Tissier: Bull. de l'Acad. de méd., Paris, 1916, **75,** 690.
59. Rhea: Jour. Med. Research, 1915, **32,** 471.

of these lesions to those in human beings who have succumbed to whooping cough. He warns that the interpretation of the results following experimental inoculation of the respiratory system of dogs, guinea-pigs and rabbits with *B. pertussis* cannot safely be based on histologic examination alone. *B. pertussis* must be recovered from the respiratory system of the inoculated animal and completely identified by bacteriologic methods as well as by agglutination reactions. Rhea suggests further that when the respiratory system of an animal liable to harbor *B. bronchisepticus* is experimentally inoculated with *B. pertussis*, the accompanying irritation might be followed by symptoms resulting from *B. bronchisepticus* already present and not from *B. pertussis* injected.

Complement Fixation.—Olmsted and Luttinger,[60] working with complement fixation in whooping cough, found that the most reliable antigen is obtained by autolyzing an aqueous emulsion of a twenty-four to forty-eight-hour growth of the Bordet-Gengou bacillus for eighteen to twenty-four hours at 56 C., and then shaking for several hours. An active serum, they found, sometimes gave nonspecific reactions; therefore a negative reaction given by an active serum is stronger evidence of lack of infection than is a negative reaction given by an inactive serum. About 40 per cent. of whooping-cough cases gave positive reactions when inactive serum was used, the highest percentage of positives being given by convalescent, vaccinated patients. They conclude that their results support the theory that the Bordet-Gengou bacillus is the etiologic factor in the disease, and think that the complement fixation test may be of value in the diagnosis of doubtful cases of pertussis.

Somewhat later, Povitsky and Worth[61] obtained a strongly agglutinating pertussis serum from the rabbit by ten or twelve intraperitoneal inoculations of living cultures given at seven-day intervals. Vaccines also produced agglutinins, but not as markedly as the living cultures. By agglutination tests *B. pertussis* strains can be specifically identified, according to these workers, from hemoglobinophilic bacilli, pertussis-like bacilli and *B. bronchisepticus*.

For purposes of identification, a strong serum of high titer should be used. Thirty-three per cent. of adult nonpertussis serums show agglutination in up to 1:40; 17 per cent. in up to 1:100; 40 per cent. of children's nonpertussis serums showed a reaction up to 1:40. A dilution of not less than 1:200 is necessary for a practically positive diagnosis of pertussis by the agglutination test.

60. Olmsted and Luttinger: Arch. Int. Med., 1915, **16,** 67.
61. Povitsky and Worth: Arch. Int. Med., 1916, **17,** 179.

Olmsted and Povitsky[62] confirmed the separation, by morphologic and cultural characteristics, of typical Bordet-Gengou bacilli from atypical strains and from the influenza bacillus by the complement fixation tests. Twelve strains of *B. pertussis* isolated by them from patients with pertussis gave complement fixation reactions similar to each other and similar to the two strains obtained from other laboratories.

Jacobsen and Mayer[63] conclude from their work with complement fixation, using the Bordet-Gengou bacillus as antigen, that a positive reaction means the individual has or has had whooping cough recently, while a negative reaction does not prove absence of the disease. On the basis of this they believe the Bordet-Gengou bacillus should be regarded as the specific cause of the disease.

Blood.—Mello-Leitao[64] studied the refractometric index of the blood in whooping cough as well as in measles, and believes that it permits differentiation of the former from tuberculous tracheobronchial adenopathy.

Benstz[65] tabulates the blood findings in sixty-three cases of whooping cough in infants under 1 year and children up to 6 years. There was always leukocytosis, most pronounced when bronchitic complications were present. The number of eosinophils was always below normal, while transitional and mononuclear forms were much increased, reaching 18 per cent. at the height of the disease.

Symptoms, Sequelae and Diagnosis.—Depping[66] reports two cases of intussusception as a sequel of whooping cough, both resulting fatally.

Kornmann[67] saw hematuria occur in otherwise normal urine with healthy kidneys, on an average of five days before the onset of the spasmodic cough. He believes that a toxin must have damaged the kidneys and their blood vessels.

Jacob[68] calls attention to a marked conjunctival congestion in the region of the external canthus as very suggestive of whooping cough in the earliest stages of the disease.

Morbidity and Mortality.—Eighty per cent. of all cases, according to Luttinger,[69] and 97 per cent. of all deaths are in children under 5 years of age. Fifty per cent. of patients are under 2 years of age and

62. Olmsted and Povitzky: Jour. Med. Research, 1916, **33,** 379.
63. Jacobsen and Mayer: Arch. f. Kinderh., 1915, **14,** 32.
64. Mello-Leitao: Am. Jour. Dis. Child., 1916, **11,** 214.
65. Benstz: Nederl. Tijdschr. v. Geneesk., 1916, **1,** 153.
66. Depping: U. S. Naval Med. Bull., 1916, **10,** 319.
67. Kornmann: München. med. Wchnscshr., 1915, **62,** 1422.
68. Jacob: Brit. Med. Jour., 1916, **1,** 589.
69. Luttinger: Am. Jour. Dis. Child., 1916, **12,** 290.

50 per cent. of deaths are in children under 1 year. The incidence of pertussis and the number of deaths are constantly higher in girls, 44 and 56 per cent., respectively, in the male and female sexes. Whooping cough is most common in the spring and summer, the mortality curve reaching its height in August. The actual mortality is hard to estimate, but it is probably about 1 per cent., and the death rate per 100,000 of population is about 7.

The mortality of whooping cough in the year 1915 in the registration area[70] was 8.1 per 100,000, somewhat above the lowest recorded rate, 6.5 in 1904, although far below the highest, 15.8 in 1903.

Crum[71] made a statistical study of the disease and shows that 1 per cent. of the grand total of deaths from all causes in twenty-four countries was due to whooping cough. Climate is probably of secondary importance either in the spread of the disease or in the determination of its type. Differences of race or nationality do not create either a predisposition or an immunity. The mortality is decidedly higher among female children of all ages, but not more than 2 or 3 per cent. of the total mortality occurred at the age of 5 years or over. The death rate in the first year of life is two and one-half times as great as in the second year, the disease being more fatal at young ages than measles.

Vaccine Treatment.—The prophylactic and curative effects of whooping cough vaccines have received considerable attention during the past two years. In 1916 Luttinger[69] declared that vaccines, when given early, have continued to give good results, both prophylactic and curative. In 1917 he[72] reiterates his belief in their efficacy and states that the effects obtained warrant the routine administration of pertussis vaccine for both purposes. He finds that the best time to institute curative vaccine treatment is in the first and second weeks of the paroxysmal stage. When the proper vaccine is given and the proper method of administration is employed, the disease is materially reduced in duration and severity.

Nine patients who had been given prophylactic injections did not contract pertussis, but developed subconjunctival hemorrhages. This fact, Luttinger thinks, points to the specific immunizing action of the vaccine against the paroxysms and to the likelihood that the Bordet-Gengou bacillus elaborates a toxin which acts on the walls of certain blood vessels.

The plan of treatment followed in the whooping cough clinics in

70. Jour. Am. Med. Assn., 1916, **67,** 1457.
71. Crum: Am. Jour. Pub. Health, 1915, **5,** 994.
72. Luttinger: Jour. Am. Med. Assn., 1917, **68,** 1461.

New York City,[73] consists in giving three or four subcutaneous injections, one every other day, and following this with an antipyretic mixture for three or four days. The initial dose for children under 1 year is 250 million, doubled every second day. Children over 1 year receive an initial dose of 500 million and adults 1 billion. Under this treatment the paroxysmal stage has been limited on an average to a duration of about three weeks. Prophylactic immunization has been practiced in forty-five cases with no disease among the patients treated. A fair percentage of controls became infected.

Bloom[74] gives a large initial dose, not less than 120 millions, increasing 60 million each succeeding dose, giving the maximum quantity every other day until one of the marked symptoms showed an appreciable improvement, then continuing every three or four days until cured. He found the average duration of fifteen cases to be only twenty-eight days, and that the intensity and number of the coughing spells and the vomiting lessened or ceased.

Shimer[75] found that the vaccine controlled the cough and vomiting, but that the beneficial effects rarely lasted for more than thirty-six to forty-eight hours. Its use, however, seems to shorten the length of the disease by two or more weeks. Frankel[76] injected ten babies with pertussis vaccine and none of them contracted the disease, although in constant contact with it.

The most pessimistic utterances regarding the value of the vaccines emanate from Von Sholly, Blum and Smith.[77] Their study of a series of whooping-cough cases shows that since whooping cough vaccine statistics under present conditions must be based chiefly on reports of the parents, one must be careful in accepting what they say. Their figures show that nonspecific influenza vaccine differs very little from pertussis vaccine in influencing the duration of the paroxysmal stage of the disease. Of all the cases, the shortest course was run in the nonvaccinated controls and in those receiving milk-colored water. None of the patients inoculated with either pertussis or influenza vaccines contracted the disease. Of 700 children exposed in their families, 24.8 per cent. escaped the disease, and in view of this rather large number of natural immunes, and the fact that influenza vaccines apparently act the same, they ask, can one be sure that pertussis vaccines actually confer immunity? These observers conclude that more observations and more critical observations with controls for comparison must be undertaken

73. Monthly Bull., New York Health Dept., November, 1915.
74. Bloom: New Orleans Med. and Surg. Jour., 1916, **69,** 200.
75. Shimer: Lancet-Clinic, 1916, **116,** 7.
76. Frankel: Kentucky Med. Jour., 1915, **13,** 458.
77. Von Sholly, Blum and Smith: Jour. Am. Med. Assn., 1917, **68,** 1451.

before the case can be considered made out for the curative and prophylactic value of a specific pertussis vaccine.

Other Methods of Treatment.—Hoag[78] found that in his hands sodium bromid and antipyrin gave the best results of any drugs, but he thought that vaccines seemed effective in any stage. As a prophylactic his experience has been absolutely favorable.

Polozker[79] reports on 100 cases in which various forms of treatment were tried, with little success in favorably affecting the course. His experience with the vaccine has been encouraging and he declares that he will continue its use.

Ebstein[80] has found that diathermia of the larynx, applied from each side, has a remarkable attenuating effect on whooping cough, transforming it into an ordinary cough, with which the night rest is no longer disturbed. Ordinary electricity is not enough; it must be the electric waves of the diathermia technic applied for five to ten minutes once or twice to each side of the neck with a current of 0.25 to 0.6 ampere. It causes no sensation except that of warmth, so that children do not object to it.

Doernberger[81] believes that the best means of relief from whooping cough is pure air, free from soot or dust. This is hard to obtain, and he suggests that a part of the public parks be fenced off for whooping cough children.

Benstz[65] tried many drugs, but no favorable effect was noted from most, though some beneficial action was seen after the use of extract of belladonna, from 1 to 6 mg. three times a day.

Peutz[82] injected serum from a convalescent whooping cough child into three others who seemed to be just developing the disease. A mitigating influence seemed unmistakable, but he regrets the smallness of the series.

Kraus[83] caught sputum of the first stage of whooping cough in sterile Petri dishes, washed it, examined it for tubercle bacilli, then mixed it with ether and shook it mechanically for several days. The ether was then evaporated and the fluid tested for sterility. The sterile fluid was injected subcutaneously in quantities of 1 or 2 c.c. every three or four days. Almost without exception there was improvement. The number of attacks decreased, the spasmodic cough became more catarrhal in character, the vomiting soon ceased, and hemorrhages, if present, disappeared. Kraus received an impression of great improvement from the treatment.

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78. Hoag: Am. Med., 1916, **11,** 255.
79. Polozker: Am. Jour. Obst., 1916, **73,** 551.
80. Ebstein: München. med. Wchnschr., 1916, **63,** 45.
81. Doernberger: München. med. Wchnschr., 1917, **63,** 1691.
82. Peutz: Nederl. Tijdschr. v. Geneesk., 1917, **1,** 714.
83. Kraus: Wien. klin. Wchnschr., 1915, **28,** 1405.

MEASLES

Etiology.—During a period of four years Tunnicliff[84] has blood cultured fifty patients in the preeruptive and eruptive stages of measles, and five when the rash was fading, using various mediums, both aerobic and anaerobic. A small micrococcus was observed in forty-two of the early cases, the largest number of positive cultures being obtained in semicoagulated horse serum and whole blood ascites dextrose agar shake cultures. Growth appeared in the original tubes in from one to twenty-two days. Twenty-eight of the forty-two positive cultures grew slightly for two or three generations only. One remained strictly anaerobic, while thirteen became aerobic in the second generation. The special points of interest are the almost constant presence of a diplococcus in the blood of measles patients during the preeruptive and eruptive stages; its presence alone and in large numbers before the appearance of the eruption, and alone in a large proportion at the height of the infection, and its presence at the same time in the throat, nose and eyes.

Epidemiology and Prophylaxis.—Wagener,[85] studying measles epidemics, found nothing to lead him to believe that measles can be transmitted by fomites or carriers. He clearly traced the sequence of events in one-room school houses. The pupils became infected by one or more children who had been exposed outside. Each infects those in the immediate vicinity and these in turn infect others, until by the end of the third week all have become infected. This is followed by infection of children at home of preschool age and of adults.

No child escaped the disease who was exposed for the first time after the age of 5 months. None under 4 months contracted the disease and only one of 5 months. Wagener thinks it is possible that young infants escape because they breathe only through the nose, and thus the measles germs do not have access to the throat. If the infant's nose is stopped up this protection is lost. He calls attention to the fact that 49 per cent. of persons who had already had typical measles developed symptoms on the part of the upper air passages, digestive tract, etc., while other members of the family were having measles. He believes these symptoms were due to the measles germs, and that these persons were, for the time being, carriers.

Lewis[86] believes that in attempts to control measles the carriers of convalescence must be recognized. They may be identified, according to him, by the presence of an inflammatory condition of the mucous membrane of the nose, tongue and throat.

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84. Tunnicliff: Jour. Am. Med. Assn., 1917, **68,** 1028.
85. Wagener: Monatsch. f. Kinderh., 1916, **13,** 477.
86. Lewis: Boston Med. and Surg. Jour., 1917, **176,** 742.

Curtis[87] is of the opinion that present methods of isolation, placarding, fumigating, etc., have reduced the attack rate appreciably. The question of how to exercise control of this disease, which is considered harmless by the laity, is difficult of solution, and under present conditions, probably not practicable. Public education and the discovery of some certain method of early diagnosis may solve the problem.

Whyte[88] observes that as most cases of measles are well into the eruptive stage before they are seen by the physician, any measures decided on to cope with the situation should be directed toward the control of the movements of contacts rather than to prolong isolation of the original case. Quarantine and observation of contacts for fourteen days from the date of last exposure would seem to be the only effective measure in preventing the spread from house to house. If it were possible to provide a routine examination for Koplik's spots during the second week of quarantine, many cases could be put under strict isolation during the period when such a measure would be of some value. Gray[89] believes that for the control of measles it will be necessary to educate parents to the importance of the disease, and to train teachers to recognize the prodromal symptoms. Susceptibles who have been exposed need not be restricted for seven days after contact, but should thereafter be quarantined for at least ten days.

Wilson[90] would approach the problem of measles prevention along the following lines: (1) standardization of present laws and adoption of the same by all health boards; (2) early detection of cases, to be accomplished by cooperation of the school and health authorities with the family physician; (3) a complete reform of hospital construction so that hospitalization may be made both popular and efficient; (4) a persistent effort to isolate the causative organism in order that an intelligent effort may be made to produce artificial immunity.

Immunity.—Herrman[91] says that infants under 2 months of age are absolutely immune to measles, this immunity gradually lessening until by the eighth month it has entirely disappeared. It is not conveyed through the breast milk, for artificially fed infants are also immune.[92] The gradual disappearance of immunity is shown by the lengthening of the period of incubation. Apparently only those are immune whose mothers have had the disease, and frequently those infants who are exposed at an early age without contracting the disease are not infected

87. Curtis: Am. Jour. Pub. Health, 1916, **6,** 265.
88. Whyte: Canada Pract. and Rev., 1916, **41,** 336.
89. Gray: Jour. Infect. Dis., 1915, **17,** 559.
90. Wilson: Arch. Pediat., 1917, **34,** 241.
91. Herrman: Am. Jour. Obst., 1916, **74,** 551.
92. Herrman: Arch. Pediat., 1917, **34,** 38.

when exposed in later life. Herrman[93] attempted to immunize artificially forty infants under 5 months of age by inoculating the nasal mucous membrane with mucus collected from otherwise healthy children, taken twenty-four hours before the measles eruption appeared. The majority showed no distinct reaction, fifteen showed a slight rise of temperature, and in a few instances a small number of spots were noted on the face and body. Of the forty inoculated, four now over a year old have come in contact with cases of measles and have not contracted the disease. Two were reinoculated at the age of 21 and 23 months, respectively, with negative results.

Signs and Symptoms.—Gray[89] studied an epidemic of 254 cases of measles and found that the minimum period from exposure to the first symptom was seven days, the maximal fourteen days and the average eleven days. The minimal period from the first symptom to the appearance of the exanthem was one day, the maximal seven days and the average three days. The minimal period from exposure to the appearance of the exanthem was eleven days, the maximal nineteen days, the average thirteen and a half days. The incidence of the disease was greatest in males at 6 years of age, and in females at 8 years.

Gardner[94] thinks that the tongue of measles is characteristic. It is glazed, with a moderately heavy dull-white furring down the center. On the posterior half this deepens to a heavier dirty brown. The central coating of the anterior portion thins toward the edge, becoming an inflammatory red, with elevated and redder papillae. The appearance of the tongue was noted earlier than any other symptom.

Mello-Leitao,[64] studying the refractometric index of the blood in measles, believes it to be of value in differentiating that disease from rubella.

Complications and Sequelae.—Wilson[95] studied 2,000 cases of measles in the Contagious Hospital at Ellis Island and concludes that cross infection, especially that of diphtheria, is the most serious event that can occur in measles. Suppurative otitis media, although the most frequent complication, is not of grave import when properly treated. Bronchopneumonia complicated about 10 per cent. of all measles cases, being but little influenced by weather conditions in the frequency of its occurrence or its fatality. The fatality of measles complicated by bronchopneumonia was 58 per cent., but this varied in an exceedingly erratic manner and without marked relation to the total case fatality of the disease. Wilson came to the conclusion that the incidence rate of bronchopneumonia as a complication, rather than its case mortality,

93. Herrman: Am. Jour. Obst., 1915, **72**, 739.
94. Gardner: Am. Jour. Clin. Med., 1916, **23**, 925.
95. Wilson: Med. Rec., New York, 1916, **84**, 756.

appeared to be an index to the severity of any particular outbreak of measles.

Dupuy[96] finds that 10 per cent. of measles patients suffer from middle ear abscesses. He gives a few whiffs of ethyl chlorid in children over 2 years old in order to perform a technically perfect tympanotomy. Whenever the ears are suspected, Dupuy opens both drums. He found every drum to be off-colored, slightly hyperemic, during the last epidemic. This shows how easily the integrity of the middle ear becomes disturbed during an attack of measles.

Case Reports.—Secher[97] reports that thirteen out of thirty-one children affected with measles suffered from an enteritis which he believes was the result of the localization of the disease in the bowels. In seven the enteritis was quite severe and two of the children died. Bacteriologic findings were negative. Eaton and Woods[98] report two cases of measles complicated by whooping cough, death occurring in one, possibly from pneumonia. Opdyke[99] saw measles in a 7-year-old girl, which followed an attack of whooping cough and influenza and which was complicated by a fatal mastoiditis and meningitis. Moore[100] describes a case of acute generalized tuberculosis with left oculomotor paralysis occurring after an attack of measles.

Winter[101] reports two cases of measles exanthemata in infants 16 and 18 days old, respectively, in whom there was a history of typical prodromata a day before. Winter comments that since we know that the prodromal and incubation stage of measles is thirteen to sixteen days, and only exceptionally longer, one has to admit that in both instances the infection occurred in extra-uterine life, in the first case most probably on the first day of life, and in the second, most probably on the first to third day. This observation disproves the contention that the new-born are immune to exogenous infections.

Sainton[102] speaks of a case of severe inflammation of the anterior half of the tongue (hemiglossitis) complicating measles.

Mortality.—Boudreau[103] shows that measles causes about twice the number of deaths every year in Ohio that scarlet fever does, and that the case-fatality rate is very high under 5 years, being as high as 25 per cent., and very low over 10 years, less than 1 per cent.

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96. Dupuy: New Orleans Med. and Surg. Jour., 1917, **69,** 741.
97. Secher: Berl. klin. Wchnschr., 1916, **53,** 250.
98. Eaton and Woods: Arch. Pediat., 1916, **33,** 513.
99. Opdyke: New York Med. Jour., 1916, **103,** 986.
100. Moore: Dublin Jour. Med. Sc., 1916, **141,** 174.
101. Winter: Jahrb. f. Kinderh., 1915, **81,** 465.
102. Sainton: Bull. et mém. Soc. méd. d. hôp. de Paris, 1916, **40,** 709.
103. Boudreau: Ohio State Med. Jour., 1916, **12,** 104.

The death rate for 1915 in the registration area for measles was 5.4 per 100,000 of population, the lowest since 1900.[104]

Treatment.—Longin[105] treated more than 100 cases of malignant measles with intravenous injections of colloidal gold. The mortality among these patients ranged from 3 to 5 per cent., whereas the mortality for the epidemic as a whole was 12 per cent. Longin believes that the striking results, especially the rapid subsidence of the temperature and pulse and the continuation of the great improvement, are the result of the medication.

Place[106] protests against the unhygienic manner in which measles patients are often treated and urges that the medical profession substitute for the irrational and often harmful ideas of management a sensible, rational and scientific handling of the disease. He believes that disinfection is of no value and that isolation is helpful only if it can be applied thoroughly.

Experimenting with ethylhydrocuprein, Hirschfelder and Schultz[107] obtained negative results in scarlet fever, but in measles the effect seemed more promising. Eleven treated cases averaged 4.3 days, while the average of ten untreated cases was 7.9 days. This would indicate that the drug is worthy of further trial.

SCARLET FEVER

Epidemiology and Prophylaxis.—Hubbard[108] thinks that there is no such thing as controlling scarlet fever, at least in New York City. Isolation as formerly practiced in that city was not satisfactory, so trained nurses were substituted for medical inspectors, the former combining social welfare work with the duties of establishing isolation, and the change has been highly successful. In New York City they regard the patient as the original source of infection and concentrate their efforts there. The most frequent carriers of infection, they think, are the patient, persons coming into contact with the latter, and lastly, the patient's surroundings, the bedding, room, clothing, etc. This being accepted, control must be exercised by isolation continued until every possible danger for the public has passed.

From his recent experiences during an epidemic of scarlet fever in Amsterdam, Heijermans[109] wonders whether isolation and placarding are the best means of prophylaxis in scarlet fever. They do not seem to check the disease and apparently are not effective as at present

104. Jour. Am. Med. Assn., 1916, **67,** 1457.
105. Longin: Med. Press and Circ., 1916, **102,** 184.
106. Place: Boston Med. and Surg. Jour., 1916, **175,** 704.
107. Hirschfelder and Schultz: Am. Jour. Dis. Child., 1916, **11,** 360.
108. Hubbard: Med. Rec., New York, 1916, **84,** 490.
109. Heijermans: Nederl. Tijdschr. v. Geneesk., 1916, **2,** 1719.

applied. He advocates notification of cases, but no placarding of houses. Heijermans is not in favor of hospitalization, believing that it is better to keep the children at home, reserving the hospital for the cases of exceptional severity. Many children are sent there who do not have the disease, a positive diagnosis being doubtful. Further, there is no evidence that institutional treatment wards off complications.

Ekholm[110] found that in the last twenty years, 50 per cent. of the buildings in his city have had no cases of scarlet fever in them. In other buildings the disease occurred again and again. There were twenty-three return cases following dismissal of 724 patients from the hospital as cured. Ekholm makes the significant statement that walking cases without eruption are probably responsible in many instances for the spread of the disease.

Boudreau[103] outlines the prevention of scarlet fever as depending on the following: (1) skilful and conscientious physicians; (2) well organized health departments; (3) contagious disease hospitals; (4) public health nurses to visit cases; (5) physical supervision of schoolchildren; (6) cooperation of an enlightened public; (7) supervision of the milk supply.

Chesley[111] says that one of the essentials in the control of the disease is the follow-up and supervision of exposed persons, as well as inspection of schoolchildren, the follow-up of absentees and the tracing of the source of infection. In his opinion desquamation is no objection to terminating isolation. Chesley thinks that hospitalization or isolation in care of a trained attendant is preferable to house isolation. Ker[112] pays no attention to scarlet desquamation and regards a minimum detention period of four weeks as an indication of a welcome change in responsible medical opinion, and hopes that at the present moment, when all are asked to be economical, health authorities will take advantage of this change in order to reduce hospital expenditures.

Chapin[113] believes that the hospital as a factor in exterminating scarlet fever has been disappointing. Even the usual methods of home isolation are not of great value. The disease is still very prevalent and is only slowly decreasing. No doubt more intensive work in ferreting out the mild cases as sources of infection would do much toward reducing the prevalence of the disease, especially in small communities. Chapin emphasizes that the ideal to be strived for is the isolation of more cases, not more isolation of the cases. Too much should not be attempted in the isolation of the case in the family. If 40 or 50 per

110. Ekholm: Finska Lakar. Handl., 1915, **57,** 5.
111. Chesley: Am. Jour. Pub. Health, 1916, **6,** 234.
112. Ker: Lancet, London, 1916, **1,** 481.
113. Chapin: Boston Med. and Surg. Jour., 1916, **175,** 715.

cent. of the cases could be isolated in hospitals, the full value of the latter would be secured.

Ringeling,[114] studying the cases of scarlet fever in Amsterdam, concludes that not much can be anticipated from hospital treatment of the disease in general prophylaxis, especially since healthy bacillus carriers cannot be isolated. He attributes the low mortality to prompt hospitalization, quoting London statistics to the effect that in 1890, 42.8 per cent. of the cases were in hospitals, with a mortality of 5.6 per cent.; in 1910, 85.6 per cent. were hospitalized, with a mortality of 2 per cent.

Lewis[115] thinks that he has practically abolished recurrent cases of scarlet fever, made secondary cases infrequent and lessened reported cases, by isolating the carriers of convalescence and the carriers previously having had the disease. In his opinion the control of scarlet fever will be found to lie in the supervision of those who have previously had the disease, at and during those periods when with recurrent infections they again show the buccal-pharyngeal signs of the disease.

In a later communication Lewis[116] indicates that throat cultures in scarlet fever frequently give the same aid as in diphtheria. He finds that a certain streptococcus, morphologically, gives reliable data, and he uses the appearance of this streptococcus as a cause for search for either acute cases or carriers in an endeavor to control the disease. He thinks that over a period of one and half years the method has proved its value most exactly.

Broadbent[117] reports a case of what he regards as a scarlet fever carrier.

Etiology.—Not a great deal of experimental work on the bacteriology of scarlet fever has been done in the past two years, but two entirely different organisms have been brought forward as the cause of the disease. Mallory and Medlar[118] found a gram-positive bacillus which they think is the causative organism, while Mair[119] of Cambridge reports a diplococcus as responsible.

Mallory and Medlar found their gram-positive bacillus postmortem in the crypts of the tonsils, in the exudation on the tonsils, and in almost pure culture in slight depressions and erosions in the squamous epithelium covering the tonsils, the pillars of the fauces, the soft palate, including the palate and the root of the tongue. Along the surface and in the upper part of the exudation in the trachea similar masses

114. Ringeling: Nederl. Tijdschr. v. Geneesk., 1916, **2,** 1874.
115. Lewis: Boston Med. and Surg. Jour., 1916, **175,** 683.
116. Lewis: Boston Med. and Surg. Jour., 1917, **176,** 170.
117. Broadbent: Lancet, London, 1916, **2,** 121.
118. Mallory and Medlar: Jour. Med. Research, 1916, **34,** 127.
119. Mair: Jour. Path. and Bacteriol., 1916, **20,** 366.

are found, as well as along the basement membrane of the same region. They were also found in the bronchioles and alveoli of a bronchopneumonic lung. The organism was found in the tissues of eight persons dying of the disease and in smears and cultures from the tonsils, soft palate, pharynx and nasopharynx of sixty patients. The bacillus is strongly gram-positive, in culture being slightly smaller than the diphtheria bacillus and varying from coccus-like to large bacillary forms. Pairs and short chains are common, while in the water of condensation long chains are found. The organisms isolated are facultative aerobes, growing best on serum glycerin. Mallory and Medlar[120] conclude that it is reasonable to infer that scarlet fever may be due to a strongly gram-positive bacillus which is less virulent than *B. diphtheriae* and which infects practically the same localities. Fibrin formation is absent or slight, and on this account primary gross lesions are inconspicuous. There is no membrane formation unless due to secondary streptococcus invasion. The toxin of this organism causes necrosis of the epithelial layers and occasionally of the deeper tissues, leading to an exudate of serum and polymorphonuclear leukocytes. In uncomplicated fulminant cases the causative organism is present in large numbers in the lesions in the respiratory tract up to the time of death, but in milder cases they seem to die out quickly, so that by the second or third day after the eruption they are impossible of demonstration. Under certain conditions they may persist for weeks, the patient becoming a scarlet fever carrier.

Secondary infection with streptococci is common and death is occasionally due to them rather than to the bacillus of scarlet fever. The eruption and the nephritis are both probably of toxic origin.

The organism believed by Mair to be responsible for scarlet fever is a diplococcus, which can be demonstrated, according to him, in the throats of scarlet fever patients during the first week of the disease in 87 per cent. of cases. It disappears usually about the fifth week of convalescence, but in some patients persists much longer.

In monkeys the diplococcus produces a disease resembling scarlet fever, but it has little tendency to produce septicemia. Mair found it confined to the region of primary invasion, usually the throat, and there it produces toxins which are poured into the blood stream. Scarlatinal arthritis is a feature common to the disease in both man and monkeys. No definite evidence of nephritis has yet been found in the monkey, nor does the rash occur.

Additional evidence in support of the diplococcal theory is found in the fact that complement fixation reactions occur with much greater frequency and with greater intensity in scarlet fever than in control

120. Mallory and Medlar: Jour. Med. Research, 1916, **35,** 209.

cases. This observation is against the view that the diplococcus is a secondary invader.

Schleissner[121] experimented with streptococci, blowing a twenty-four-hour culture of scarlet fever streptococci into the noses and mouths of monkeys. This was followed by fever, angina, enanthem and strawberry tongue, and after ten days there was desquamation in large flakes. Attempts at reinfection was unsuccessful, so there seemed to be an immunity developed. Attempts to infect with germ-free bouillon cultures were unsuccessful.

These facts make it highly probable, in Schleissner's opinion, that this scarlet fever streptococcus is the specific cause of the disease.

Watson[122] calls attention to the close similarity of complications and sequelae in rheumatic fever, scarlet fever and malignant endocarditis, and suggests that there is a common factor in their cause. The blood changes in these three diseases are the same, a polymorphonuclear leukocytosis in each. Watson feels justified in concluding that in all these cases there is a septic infection of the lymphoid tissues in the region of Peyer's patches. Further than that, he believes that every symptom of scarlet fever points to an acute intestinal catarrh, fatal in malignant cases and productive of intense irritation in those of ordinary severity.

Serum Reactions.—Dick and Dick,[123] by the use of complement fixation tests, were unable to demonstrate any specific scarlatinal virus or antigen in the blood serum or in extracts of spleen or lymph glands. Fixation tests with throat mucus as antigen gave in one instance a weak fixation of complement with the serum of a convalescent scarlet fever patient. They found that the toxicity of human blood serum for guinea-pigs is increased during the acute stage of scarlet fever. Positive Wassermann reactions in scarlet fever obtained with the acetone-insoluble portion of alcoholic heart extract are strongly suggestive of syphilis.

On the supposition that the weakly positive complement-fixation reaction, using mucus from a scarlatinal angina as antigen, was due to a micro-organism capable of growth, cultures were made of the mucus and tested as to antigenic properties by means of complement fixation and intracutaneous tests.[124] These cultures showed the presence of an antigen which reacted with scarlatinal serum to fix complement in more than half the cases tested, whereas controls gave positive reactions in over one-third of the cases tested. Comparing the antigenic property of streptococci with that of the mixed cultures

121. Schleissner: Jahrb. f. Kinderh., 1915, **82,** 225.
122. Watson: Glasgow Med. Jour., 1915, **84,** 401.
123. Dick and Dick: Jour. Infect. Dis., 1916, **19,** 175.
124. Dick and Dick: Jour. Infect. Dis., 1916, **19,** 638.

of the preceding experiment, the results obtained would indicate that no antigenic properties need be assumed in any of the antigens prepared from scarlatinal throats, other than that of the streptococci present.

Cutaneous tests were also carried out, using a heat-killed culture of mucus from scarlatinal throats, with a pure culture of a hemolytic streptococcus from a fatal scarlatinal angina and a milk and whey culture from an ordinary tonsillitis. Any specificity comparable to the tuberculin cutaneous test could not be demonstrated.

Symptoms.—Berg[125] classifies the severe scarlet fever cases into the toxic, the toxic hemorrhagic and the septic. The prognosis in the septic type is better than in the toxic, but true hemorrhagic cases are invariably fatal. Berg believes that the so-called scarlatina accompanying burns, surgical injuries and the puerperal states is not scarlet fever, but a symptom of sepsis.

Ostrovsky[126] found that in the initial stage of scarlet fever there is retention of chlorids and that from the tenth to the twentieth day the amount eliminated rises in waves.

Gauss[127] studied the spinal fluids from fifty cases of scarlet fever and "associated exanthems," and found them all sterile, with the exception of four contaminations. The pressure varied with the mental and physical attitude of the patient. The cell count varied from 1 to 29 cells per cubic centimeter, averaging 8 cells.

Traumatic and Pseudoscarlet Fever.—Korach[128] reports the case of a physician who casually excoriated one hand and was then exposed to scarlet fever. In forty-eight hours he developed a typical scarlet fever lymphangitis and by the third day he presented the general symptoms of scarlet fever with the rash.

Frankel[129] has observed among children numerous cases which, although resembling scarlet fever, differ from it essentially, and etiologically seem to be more nearly related to influenza. The onset is usually sudden, with elevation of temperature and a scarlatiniform rash, but the course is milder and the rash paler, more evanescent and is followed by more minute desquamation. Frankel hopes to focus attention on these cases and urges their investigation by those equipped for research work.

Lasalle[130] reports a case of pseudoscarlatina of toxic origin, probably due to copper sulphate.

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125. Berg: Am. Jour. Obst., 1915, **72,** 1074.
126. Ostrovsky: Russk. Vrach, 1916, **15,** 7.
127. Gauss: Jour. Am. Med. Assn., 1917, **68,** 779.
128. Korach: Deutsch. med. Wchnschr., 1917, **43,** 12.
129. Frankel: New York Med. Jour., 1916, **104,** 799.
130. Lasalle: Arch. de méd. d. enf., 1916, **19,** 91.

Morbidity and Mortality.—Dublin[131] studied the complete records of 1,153 cases of scarlet fever. Nearly 82 per cent. were among children between 2 and 10 years of age, the greatest predisposition being found between 3 and 7 years of age. The death rate was 7.8 per cent. for the series, 15.5 per cent. occurring during the second year. Ninety-two per cent. of all deaths were in children under 10 years of age.

Tracing the 1,063 patients who survived, and who were under observation for an average period of 3.4 years, he found that only eighteen deaths occurred, whereas 18.6 deaths were expected. The actual mortality, then, was 97 per cent. of the expected, as compared with a mortality in those surviving an attack of typhoid fever twice as great as was to be expected.

Of the eighteen deaths, three patients died of endocarditis, five of respiratory diseases and four from tuberculosis. There were no deaths from kidney disease. Generally speaking, the death rate for colored children was about one-fourth that of white children.

Donnally,[132] in a study of the morbidity and fatality of scarlet fever based on several million cases, concludes that periodicity in the appearance of epidemics cannot be made out; that a decline in morbidity cannot be generally demonstrated; that the sexes as a whole show equal susceptibility; that about two children out of three between 3 and 8 years of age contract scarlet fever if exposed to the disease in their homes, if they have not previously had it; that it appears to be a milder affection than formerly, but that epidemics may vary greatly in virulence and have been attended by greater fatality in some places than in others.

Ostheimer[133] says that 1,072 cases of scarlet fever were reported from Philadelphia in 1915, less than one-third the number reported in 1913. This is a morbidity rate of 63.7 per 100,000 as compared with 208 in 1913. Of the patients, 74.6 per cent. were treated in hospitals, the death rate for the entire city being 2.4 per cent.

The death rate from scarlet fever in the registration area[134] in 1915 was 3.6 per 100,000 of population, the lowest since 1900.

Case Reports.—Several cases of interest are reported by different observers. Iglauer[135] reports a rare complication, a case of esophageal stenosis, which he dilated by a method of his own, the latter being fully described; Lynah,[136] a case of osteomyelitis of the sinuses of the

131. Dublin: Jour. Am. Med. Assn., 1916, **66,** 1667.
132. Donnally: Am. Jour. Dis. Child., 1916, **12,** 205.
133. Ostheimer: Am. Jour. Pub. Health, 1916, **6,** 1104.
134. Jour. Am. Med. Assn., 1916, **67,** 1457.
135. Iglauer: Lancet-Clinic, 1916, **115,** 289.
136. Lynah: Laryngoscope, 1917, **27,** 176.

nose, with apparent recovery; Cooke[137] reports six cases of hyperthyroidism occurring after mild scarlet fever, all in males, within a period of four months, and all in the same ward. He suggests that a microbic infection was responsible. Lortat-Jacob and Oppenheim[138] believe that a comparison of the symptoms shown by their patient with those of postscarlatinal paresis confirms the assumption that cerebral arteritis is responsible for the chronic infectious hemiplegia in such conditions. Miller[139] speaks of a case apparently exhibiting measles and scarlet fever simultaneously, while three other children in the family had measles alone. Smith[140] cites what he believes was an instance of three attacks of scarlet fever in the same child within a year. Squibbs[141] tells of a relapsing scarlet with general glandular enlargement.

Nobécourt, Jurie des Camiers and Tournier[142] report several cases of scarlet fever complicated by articular rheumatism, endocarditis and pericarditis. The same observers[143] saw two cases of phlebitis during the course of scarlatina. Ramond and Chambas[144] report icterus as occurring in 8 per cent. of 131 cases of scarlet fever seen by them. Creyx[145] saw a case with a combined scarlatinal and scarlatiniform rash.

Clough[146] reports a very interesting instance of postscarlatinal anuria in a child of 7, in whom, with one exception, the daily output of urine was never more than 4 ounces over a period of thirty-four days. Only 91 ounces were passed from March 23 to May 7. Only once were two casts found in the urine, and no albumin was present at any time. No sort of treatment had any effect on the condition, but the child at the time of the report was in perfect health.

Ramond and Schultz[147] call attention to neuralgias seen during the early days of scarlet fever, while Hutinel[148] discusses at length the pneumonias of scarlatina. Florand and Merklan[149] remark on the fre-

137. Cooke: Jour. Roy. Army Med. Corps, 1916, **27**, 114.
138. Lortat-Jacob and Oppenheim: Progrès méd., 1916, **31**, 213.
139. Miller: Arch. Pediat., 1917, **34**, 138.
140. Smith: Brit. Med. Jour., 1915, **1**, 1003.
141. Squibbs: Med. Times, 1915, **43**, 745.
142. Nobécourt, Jurie des Camiers and Tournier: Bull. et mém. Soc. méd. d. hôp. de Paris, 1915, **39**, 779.
143. Nobécourt, Jurie des Camiers and Tournier: Bull. et mém. Soc. méd. d. hôp. de Paris, 1915, **39**, 807.
144. Ramond and Chambas: Bull. et mém. Soc. méd. d. hôp. de Paris, 1915, **39**, 770.
145. Creyx: Jour. de méd. de Bordeaux, 1917, **88**, 30.
146. Clough: Am. Jour. Dis. Child., 1916, **11**, 367.
147. Ramond and Schultz: Bull. et mém. Soc. méd. d. hôp. de Paris, 1916, **40**, 298.
148. Hutinel: Arch. de méd. d. enf., 1916, **19**, 57.
149. Florand and Merklan: Bull. et mém. Soc. méd. d. hôp. de Paris, 1916, **40**, 985.

quency of rheumatism in scarlet fever and state that it is of the chronic arthralgic type. It frequently undergoes spontaneous cure. The heart should frequently be examined during scarlatina, as cardiac involvement frequently occurs, endocarditis with murmurs, symptoms of passing myocarditis, etc.

Liddell and Tangye[150] cite a case of supposed intra-uterine scarlet fever. Four of five children in a family developed the disease, the mother being confined eleven days after the removal of the children to the hospital. After a thorough washing, which removed all traces of lanugo, the trunk and limbs of the new-born infant were found to be desquamating freely. This lasted for several days and the urine showed distinct traces of albumin. The mother had been rather unwell during the last week of pregnancy, but had no sore throat or rash and her temperature was normal.

Haeggstrom's[151] patient developed otitis media during scarlet fever, necessitating an operation on the second day for mastoiditis. Six days later there was a profuse hemorrhage from which the child died. Necropsy showed the side wall of the sigmoid sinus to be completely eroded. Twenty-five similar cases were found in the literature.

Wilson[152] is impressed with the mental apathy which children in the Contagious Disease Hospital at Ellis Island often exhibit during convalescence from scarlet fever and measles. He reports a case showing catatonic postures.

Prophylactic Vaccination.—Di Cristina[153] prepared a vaccine with 15 c.c. of convalescent serum and 10 gm. of desquamated shreds and scales, adding 0.8 per cent. phenol and 1 c.c. of guinea-pig complement, incubating for fifteen hours at 37 C. One c.c. of this vaccine was given subcutaneously every second day, from 0.75 to 4 c.c. in all. By the second or third injection the specific deviation of complement occurred.

The children thus treated had all been casually exposed to scarlet fever, but none of them developed the disease. Encouraged by this success, he left some of the vaccinated children in the scarlet fever ward for several days. Other children had been placed in this same ward by mistake. They were vaccinated after twenty-four hours' exposure and then allowed to sleep with patients in the eruptive stage and in the desquamative stage, but none of the vaccinated children developed the disease, even when kept in bed with scarlet fever sufferers for several days. Di Cristina declares that there is something in the scales which confers immunity on healthy children, the immunity

150. Liddell and Tangye: Brit. Med. Jour., 1916, **2,** 389.
151. Haeggstrom: Hygiea, 1916, **79,** 58.
152. Wilson: Jour. Abnormal Psychol., 1916, **11,** 123.
153. Di Cristina: Pediatrics, 1916, **67,** 385.

thus induced being rendered manifest by the deviation of complement test.

Serum Treatment.—Additional reported cases confirm Reiss and Hertz'[154] opinion as to the great value of convalescent serum in scarlet fever, which in many cases saves life. They found it necessary to give the serum intravenously and in large doses, at least 50 c.c. in children and 100 c.c. in adults, though the gravity of the case and the day of the disease should be taken into consideration. Cases that were injected as late as the fourth or fifth day gave no prompt results.

Concerning normal serum, there is no doubt that occasionally action similar to that of convalescent serum was observed. The action of Moser's serum was very similar to that of convalescent serum. Normal horse serum seems to have no effect on scarlet fever, while the danger of serum disease speaks for the use of serum from convalescents.

The indication for the use of the serum is the appearance of scarlatina gravissima, when in a few days a picture of severe scarlet fever intoxication occurs, especially with a small, irregular pulse, cyanosis, stupor or delirium. Those cases in which a serious picture develops, due to secondary infection, are unsuitable for this treatment; for example, necrotic angina, suppurative cervical adenitis, lung complications, endocarditis, uremia, etc. The sooner the injection is made the better are the results, after the fourth or fifth day the serum rarely having any effect.

Zingher[155] treated severe forms of scarlet fever with intramuscular injections of fresh human blood, either convalescent or normal. In a number in whom the outlook was doubtful if not poor, 6 or 8 ounces of blood seemed to have a life-saving effect and encourages him to recommend the treatment in the severer forms of the disease. In nine septic or toxic cases treated with 3 to 8 ounces of whole blood obtained from three to six weeks convalescents, there was, in some, a critical drop in temperature within twelve to twenty-four hours, together with a distinct improvement in the pulse and general condition. Two patients died from the advanced septic state.

Zingher[156] favors the use of whole blood rather than serum, because of the loss of 60 per cent. of the blood with the latter method. The treatment is easily carried out, is quite harmless, and can be done by the general practitioner. He believes that the rational element in the use of convalescent serum is quite apparent, while that in the use of fresh normal blood is found in the clinical observations of its empirical value, and also in the great nutritive value of homologous blood, its marked stimulating properties, and its well-known antibody content.

154. Reiss and Hertz: München, med. Wchnschr., 1915, **62,** 1177.
155. Zingher: Med. Rec., New York, 1915, **88,** 335.
156. Zingher: Jour. Am. Med. Assn., 1915, **65,** 875.

A year later Zingher,[157] in a third communication, reports further experience with the method. He used fresh whole blood from a convalescent donor injected into the patient's muscles, either directly or after citrating. Fourteen patients with toxic scarlet fever, in whom the prognosis was doubtful or absolutely poor, were injected in amounts varying from 75 to 250 c.c., depending on the age of the patient. Of the fourteen patients injected, four died. In the remaining ten there appeared to be a distinctly favorable influence on the course of the disease. In those not complicated by a streptococcus exudate or cervical adenitis, there was a distinct critical drop in temperature. Even in the septic forms of the disease there was seen an improvement in the general condition. Larger quantities, 8 to 10 ounces, of fresh blood seemed to have a distinctly beneficial effect on the disease, especially when repeated in four or five days.

Other Forms of Treatment.—Hirschfelder and Schultz,[107] experimenting with ethylhydrocuprein, obtained negative results.

Love[158] advocates the inclusion of autogenous vaccine therapy in the routine treatment of scarlatinal otorrhea and other more trifling complications. He believes that it greatly lessens the duration of the discharges and appears to effect a rapid and permanent cure without detriment to the patient.

Hutinel[159] describes malignant scarlet fever and says that through the use of epinephrin, the mortality of this form of the disease has been reduced 50 per cent.

Ramond and Schultz[160] point out that the many analogies between scarlet fever and acute rheumatism are confirmed by the benefits derived from salicylate medication. They give 6 gm. or more a day, keeping it up until the fever, etc., have subsided, usually within three days, but to be safe, the drug is given two days longer. On the fifteenth day it is resumed again, the dose reduced 1 gm. a day. This wards off complications, which are so liable to develop between the fifteenth and the twentieth days, especially tonsillitis and nephritis. The mortality under this treatment dropped to 0.25 per cent., and complications were exceptional.

In another report Ramond[161] speaks of the good effects of sodium salicylate in scarlet fever, while Esmein[162] believes salicylic acid to be of value, even against nephritis.

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157. Zingher: New York State Jour. Med., 1916, **16,** 112.
158. Love: Jour. State Med., 1915, **23,** 202.
159. Hutinel: Med. Press and Circ., 1915, **100,** 166.
160. Ramond and Schultz: Bull. et mém. Soc. méd. d. hôp. de Paris, 1916, **32,** 866.
161. Ramond: Bull. et mém. Soc. méd. d. hôp. de Paris, 1915, **39,** 869.
162. Esmein: Bull. et mém. Soc. méd. d. hôp. de Paris, 1916, **40,** 140.

DIPHTHERIA

Epidemiology.—Crum[163] says that diphtheria is perhaps as prevalent today from the viewpoint of its worldwide distribution as it has ever been, there being reason to believe that it is still spreading geographically and tending to become endemic in the remoter sections of the earth. Some practical means of removing or effectually opposing the underlying conditions favorable to the spread of the disease must be sought for. It must be admitted that many of the possibly very important underlying conditions favoring its spread are not well understood.

Despite all that is known regarding diphtheria, the incidence of the disease, says Perkins,[164] has not materially decreased. Why such lack of success? Because in diphtheria we have a disease the virus of which is transmitted by very direct contact through the personal element, a factor difficult of control, in contradistinction to our ability to control inanimate objects which are responsible chiefly for the spread of typhoid fever. There will be no very material decrease in the incidence of diphtheria until public opinion will permit health departments to establish the percentage and distribution of diphtheria nonimmunes.

Control of Epidemics.—Brooks[165] reports the control of a long standing epidemic of diphtheria in a city of 54,000 inhabitants, the activities including culturing of school children and contacts, control of carriers, close supervision and enforcement of rational isolation, hospitalization when necessary, and the seeking out of unreported cases. Brooks concludes that, generally speaking, the communicable disease rate of any municipality indicates the degree of effectiveness of health activities, and he feels there is serious need of stimulation of civic consciousness and of education to the need of intelligent cooperation, if health is to be protected.

Benz[166] believes that from his experience diphtheria can be held to a minimum in the schools only by continued and repeated cultures of all suspected cases. In order to control a localized epidemic of diphtheria in a school, Stovall[167] immunized all who had a positive Schick reaction and isolated those with positive cultures. No further cases developed.

Lewis[168] first endeavored to control diphtheria outbreaks by controlling contacts and convalescents bacteriologically. He found, how-

163. Crum: Am. Jour. Pub. Health, 1917, **7,** 445.
164. Perkins: Ohio State Med. Jour., 1917, **13,** 89.
165. Brooks: New York State Jour. Med., 1917, **17,** 295.
166. Benz: Penn. Med. Jour., 1917, **20,** 395.
167. Stovall: Jour. Am. Med. Assn., 1917, **68,** 1089.
168. Lewis: Jour. Am. Med. Assn., 1916, **66,** 1535.

ever, that not a single case could be traced to infection from those in whom physical examination gave a negative, and culture a positive, result. As a result, no contacts were isolated if the pharynx was normal, even though cultures were positive. Combined with a neighborhood survey for missed cases and carriers, the procedure resulted in a notable decrease of diphtheria.

Moffitt[169] takes exception to the statement that in 95 per cent. of cases no Klebs-Loeffler bacilli were found after two weeks, and in 98 per cent. none after four weeks. He found that but 68 per cent. were negative at the end of three weeks and 76 per cent. at the end of four weeks. For that reason he believes that isolation should not be terminated until negative cultures have been obtained.

To prevent the occurrence of diphtheria in hospital wards Adams and Leech[170] would keep new cases in detention for five days, after having nose and throat cultures taken. Infants should be kept isolated from children of the run-about age and visiting should be restricted to adult patients.

Virulence of Diphtheria Bacilli.—Studying cultures of diphtheria bacilli for acid production with various carbohydrates in order to determine the practical value of these tests in aiding differentiation among the members of the diphtheria group, Kolmer and Moshage[171] found that acid production tests are not sufficiently regular to be depended on in determining the harmfulness of a given culture. They are of most value in the study of the solid varieties of diphtheria-like bacilli; cultures proving nonvirulent for guinea-pigs and producing no acid with sugars, are classified as Hofmann's type; nonvirulent cultures producing acid with one or more sugars are regarded as nonvirulent diphtheria bacilli.

The same workers[172] studied the question of the possible relationship between the toxin and the carbohydrate-splitting process, concluding that carbohydrate fermentation by diphtheria bacilli is dependent on secretory enzymic products of the organism, but is independent of the soluble toxin. The carbohydrate-splitting products are most likely, however, to be formed by toxin-producing bacilli.

Cary[173] also worked on acid production in carbohydrates and found that there was a maximal acid production for each strain of diphtheria bacilli in various carbohydrates, the rapidity of production varying with the greater relative exposure to air, the time varying not only with the carbohydrate, but with the different strains. Cary could not

169. Moffitt: Penn. Med. Jour., 1915, **19,** 23.
170. Adams and Leech: Am. Jour. Obst., 1916, **74,** 556.
171. Kolmer and Moshage: Jour. Infect. Dis., 1916, **19,** 19.
172. Kolmer and Moshage: Jour. Infect. Dis., 1916, **19,** 28.
173. Cary: Jour. Infect. Dis., 1917, **20,** 244.

demonstrate any constant relationship between virulence and the fermentation reactions. The number of organisms necessary for a fatal result is a good indication of virulence, but gives no idea of the toxicity of the strain.

Weaver[174] states that diphtheria bacilli from patients with diphtheria and carriers who have been in contact with such patients are practically always virulent, and usually remain so up to the time of disappearance, even after a long time. He urges that carriers be isolated until the organisms disappear or are proved to be nonvirulent.

Kolmer, Woody and Moshage[175] find virulence tests to be useful in the management of diphtheria carriers, especially from the standpoint of the duration of isolation. The tests must be sufficiently delicate to detect low degrees of virulence and must be economical and as speedy as consistent with specificity and delicacy. The best results were obtained with the subcutaneous injection of 4 c.c. of a good twenty-four-hour culture of diphtheria bacilli on Loeffler's serum. In 1,054 tests barred bacilli were found of equal virulence with the granular types, the latter being virulent in about 70 per cent. of cultures. Long solid bacilli were virulent in about 42 per cent. of cases, while short solid bacilli were uniformly nonvirulent.

Zingher and Soletsky[176] describe a new and economical method for testing the virulence of diphtheria bacilli, and Zingher[177] presents in detail an intradermal test for estimating in an economical way small amounts of antitoxin. The method is easily carried out, though it requires for accuracy a uniform technic.

Diphtheroids.—Fox[178] reviews the literature on the subject of diphtheroids and discusses it at length. There is nothing to show the origin of the nonvirulent members of that group, but that they are degraded forms is suggested. Fox[179] conducted a series of experiments in the attempt to cause mutation or degradation of diphtheria bacilli by the influence of lymph tissue and blood, but was not successful. The morphology remained quite constant except for a tendency in late generations to grow in long, clubbed, mycelial forms and these morphologic changes have probably given some observers the basis for the assumption of mutation.

Complement Fixation.—Levy[180] showed that fixation of complement by the serum of persons from a diphtheria environment occurs,

174. Weaver: Jour. Infect. Dis., 1917, **20,** 125.
175. Kolmer, Woody and Moshage: Am. Jour. Dis. Child., 1916, **11,** 257.
176. Zingher and Soletsky: Jour. Infect. Dis., 1915, **17,** 454.
177. Zingher: Jour. Infect. Dis., 1916, **19,** 557.
178. Fox: Jour. Med. Research, 1915, **32,** 325.
179. Fox: Jour. Med. Research, 1915, **32,** 309.
180. Levy: Ann. de méd., 1915, **2,** 597.

but it is seen more constantly and positively in those who have had diphtheria. They were evidently rendered immune by the presence of a bacillary focus, the products of the activity of the latter causing an ample supply of antibodies.

Culture Technic—Shimer[181] says that the advantages of the potassium tellurate medium for diphtheria cultures over the Loeffler blood serum method are an increased number of positives, a lessened number of bacteria in smears, a decrease of almost half in the time necessary to examine slides and an enormous lessening of the work necessary to obtain pure cultures.

Gehrmann[182] found that a gain in time can be expected when immediate incubation of diphtheria cultures is practiced. In his experience the body heat may be used for their incubation with perfect satisfaction.

Experimental Diphtheria Toxemia.—Bailey[183] administered large doses of toxin intravenously to the rabbit and found that it produced a pronounced vascular and parenchymatous degeneration in the kidney. Emge[184] found that a toxemia produced in guinea-pigs in such a way as to simulate the course of human diphtheria toxemia does not lead to changes in the thyroid gland to the same degree as has been observed in the human thyroid gland in fatal diphtheria. The changes seen are not sufficiently marked to permit the conclusion that this gland has a detoxicating action in experimental diphtheritic toxemia.

Diphtheria in the First Year of Life.—Analyzing 2,600 consecutive cases of diphtheria, Rolleston[185] found that less than 1 per cent. were under 1 year of age. Sixty-five per cent. of these showed nasal involvement, with or without diphtheria somewhere else, as compared with 25.6 per cent. of the total with nasal infection. Thirty per cent. were purely nasal, as compared with 1.5 per cent. of the total cases. The mortality was high, 45 per cent., as compared with 7.3 per cent. mortality among the whole number.

Laryngo-Tracheo-Bronchial Diphtheria.—Lynah[186] presents an excellent discussion of diphtheria of the tracheobronchial tree. He thinks the condition is commoner than is believed and that in the majority of cases the infection travels from below upward. As an aid to treatment the membrane should be mechanically removed through a bronchoscope by means of a small suction tube attached to a vacuum

181. Shimer: Jour. Bacteriol., 1916, **1,** 111.
182. Gehrmann: Am. Jour. Pub. Health, 1915, **5,** 1031.
183. Bailey: Jour. Exper. Med., 1917, **25,** 109.
184. Emge: Jour. Infect. Dis., 1915, **17,** 369.
185. Rolleston: Am. Jour. Dis. Child., 1916, **12,** 47.
186. Lynah: Laryngoscope, 1916, **26,** 158.

pump. After removal of the membrane the tracheobronchi are intubated with long tracheobronchial tubes. Thirty-eight cases are reported[187] with fourteen deaths.

Rolleston[188] reviews the subject of laryngeal diphtheria in adults and adds four cases of his own. He calls attention to the rarity of the condition, to its grave prognosis, to the absence or late onset of severe dyspnea, to the inefficacy of serum or other treatment and to the sudden character of the termination.

Smith[189] reports a case of primary tracheal or bronchial diphtheria, with recovery, a cast being coughed up. The diagnosis was confirmed bacteriologically. Lynah[186] remarks that he has yet to see a case of laryngeal diphtheria relieved by tracheotomy in which intubation failed.

Nasal Diphtheria.—In 3,000 cases Rolleston[190] found only fifty-five, or 1.5 per cent., of isolated nasal diphtherias, as compared with 260, or 20.6 per cent., in which nasal diphtheria was associated with an angina.

Ochsenius[191] found 88 per cent. of nasal diphtherias to be confined to one nostril. The course was always favorable, the general health being but slightly impaired.

Extra-Oral Diphtheria.—Emge[192] reports a case of primary diphtheria of the skin. Billings[193] says that there are only twenty-five cases of primary cutaneous diphtheria on record, and reports two cases, both on the fingers. Rolleston[194] reports a whitlow involving the left index, middle and ring fingers of two and a half months' duration, in the discharge from which diphtheria bacilli were found, and which healed within a week after the administration of 8,000 units of antitoxin.

Ceconi[195] saw a primary diphtheria of the vulva. Da Roche[196] tells of a case of primary localization of diphtheria on the conjunctiva. Egyedi[197] and Gaillard[198] both saw diphtheria complicate a primary syphilitic sore, one on the vulva, the other on the lip.

An interesting case of diphtheria of an abdominal gallbladder wound is related by Bristol,[199] who calls attention to the fact that

187. Lynah: Laryngoscope, 1916, **26,** 1193.
188. Rolleston: Clin. Jour., 1916, **45,** 389.
189. Smith: Brit. Med. Jour., 1915, **2,** 57.
190. Rolleston: Brit. Jour. Child. Dis., 1917, **14,** 21.
191. Ochsenius: München. med. Wchnschr., 1916, **63,** 1450.
192. Emge: Jour. Am. Med. Assn., 1915, **65,** 529.
193. Billings: Ann. Surg., 1915, **62,** 343.
194. Rolleston: Brit. Jour. Dermat., 1916, **28,** 110.
195. Ceconi: Boston Med. and Surg. Jour., 1916, **174,** 838.
196. Da Roche: Brazil-méd., 1916, **30,** 219.
197. Egyedi: Deutsch. med. Wchnschr., 1916, **42,** 1354.
198. Gaillard: Bull. et mém. Soc. méd. d. hôp. de Paris, 1915, **39,** 1036.
199. Bristol: Am. Jour. Pub. Health, 1915, **5,** 838.

because of the exposed nature, long duration and failure to recognize wound and skin diphtheria, it is especially dangerous as a source of the disease in general.

Vinsonhaler[200] reports a case of diphtheria primarily involving the sinuses, mastoid and middle ear.

Case Reports.—Knack[201] describes the occurrence of eight tonsillar abscesses among 500 cases of diphtheria, in six of which the causative organism proved to be *Streptococcus hemolyticus.* Gunson[202] reports a case of gangrene of the leg following diphtheria, the popliteal artery being found completely occluded by a thrombus. Only sixteen cases have been reported up to 1916. Lynah[203] reports a case of a safetypin in the larynx with a perilaryngeal abscess, which was diagnosed and treated as a laryngeal diphtheria. Skillern[204] tells of a diphtheritic membrane in the right lung simulating a foreign body, which was diagnosed and removed through the bronchoscope.

Downie,[205] Mason,[206] Daley and McCormack[207] and Mills and Mendelson[208] all report cases of postdiphtheritic paralysis. Barabas[209] found that in eight children out of sixteen with postdiphtheritic paralysis, sensitiveness of the skin to pain was greatly if not entirely abolished, while the sensations of heat, cold and touch were apparently not impaired. Ravaut and Krolunitsky[210] report a case of generalized diphtheritic paralysis with a meningeal reaction, evidenced by the presence of a positive albumin test and a lymphocytosis in the spinal fluid.

Gerson[211] tells of two cases of myasthenic bulbar paralysis, both in chronic diphtheria carriers, and he asks if this coincidence may not possibly explain the etiology of this affection. Gunson[212] found a crossed reflex present in 76 per cent. of cases of diphtheria. He believes that this indicates involvement of the cord in a larger number of cases than is generally recognized, and that it suggests that the motor weakness, ataxia and loss of knee jerks may be largely dependent on a central lesion of a toxic inflammatory character.

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200. Vinsonhaler: South. Med. Jour., 1916, **9,** 839.
201. Knack: Ztschr. f. Hyg. u. Infectionskr., 1915, **80,** 163.
202. Gunson: Brit. Jour. Child. Dis., 1916, **13,** 237.
203. Lynah: Laryngoscope, 1917, **27,** 93.
204. Skillern: Laryngoscope, 1917, **27,** 100.
205. Downie: Practitioner, 1915, **45,** 55.
206. Mason: Ophth. Rec., 1916, **25,** 140.
207. Daley and McCormack: Lancet, London, 1916, **1,** 915.
208. Mills and Mendelson: New York Med. Jour., 1916, **103,** 780.
209. Barabás: Jahrb. f. Kinderh., 1916, **82,** 476.
210. Ravaut and Krolunitsky: Bull. et mém. Soc. méd. d. hôp. de Paris, 1916, **40,** 913.
211. Gerson: Berl. klin. Wchnschr., 1916, **53,** 1364.
212. Gunson: Rev. Neurol. and Psychiat., 1915, **13,** 317.

Rolleston and Gunson[213] describe a case of extensive occlusion of the cerebral arteries. They analyzed eighty cases of diphtheritic hemiplegia which they were able to collect from the literature, embolism appearing to be the most common cause of that variety of lesion.

Carriers.—Weaver[174] says that observation has emphasized the fact that persistent carriage of diphtheria bacilli usually depends on some local condition, such as diseased tonsils, adenoids or sinuses, and while these carriers are less dangerous as spreaders of infection than recent cases of diphtheria, yet they must be considered as potential agents for dissemination of disease and isolated until the organisms have been shown to be nonvirulent.

Ruediger[214] thinks the carrier of great importance in transmitting the disease and advocates their isolation, unless the bacilli prove to be nonvirulent. He does not believe that it is possible to pick out carriers by mere inspection of the throat, as recently advocated by Lewis.[168]

Perkins, Miller and Ruh[215] studied diphtheria in Cleveland, with special reference to carriers. In their experience the organisms of the Hofmann type have never proved virulent, and they believe that the most satisfactory attitude towards diphtheria is that which eliminates all diphtheria-like forms as etiologic factors in the disease.

Studying the phagocytic power of the blood of diphtheria carriers, Tunnicliff[216] found it to be increased, but noted at the same time that the nose and throat may contain large numbers of leukocytes not engaged in phagocytosis. Efforts to increase the activity of these leukocytes by the use of normal serum, leukocytic suspensions, calcium chlorid, sodium salicylate, lactic acid, and magnesium chlorid, were unsuccessful, although dilute solutions of these substances are found to promote phagocytosis in vitro.

Treatment of Carriers.—Rappaport[217] reiterates that when properly applied, kaolin by its adsorptive power mechanically removes bacteria with which it comes in contact. Stress is laid on the method of application, the kaolin being first thoroughly dried, then passed through a fine flour sieve before being evenly distributed over the surface to be treated. Its action is interfered with by local pathologic conditions, removal of the tonsils and adenoids being advocated when the organisms persist unduly long in spite of kaolin.

Bell[218] suggests trying the kaolin treatment first because of its simplicity, especially in private homes, but the desired results are not

213. Rolleston and Gunson: Rev. Neurol. and Psychiat., 1915, **13,** 373.
214. Ruediger: Illinois Med. Jour., 1916, **30,** 255.
215: Perkins, Miller and Ruh: Jour Infect. Dis., 1916, **18,** 607.
216. Tunnicliff: Jour. Infect. Dis., 1916, **19,** 97.
217. Rappaport: Jour. Am. Med. Assn., 1916, **66,** 943.
218. Bell: Arch. Pediat., 1916, **33,** 836.

accomplished as quickly as with the staphylococcus spray, which, when properly applied from a laboratory and clinical standpoint, is a safe and successful method of combating diphtheria carriers.

McKay[219] reports that from an experience with thirty-six carriers treated with a bouillon culture of lactic acid bacilli there is very little shortening in the period of isolation.

Many other methods of treatment have been tried by various observers. Ott and Roy[220] report a series of seventeen carriers treated by the application of acidum carbolicum iodatum (N. F.), sixteen of which had negative cultures within eleven days. No bad results were noticed, though a thin escharotic membrane was formed at the site of application, which disappeared in forty-eight hours, leaving the throat red for a few days.

Labbe and Canat[221] believe they obtained favorable results from the insufflation of powder made from serum of horses previously injected with heat-killed diphtheria bacilli. No organisms were to be found in thirty-five cases after an average of twenty-four days of treatment, while the intervals averaged over forty days in a group treated with the ordinary antiseptic measures. Beattie, Lewis and Gee[222] experimented with hypochlorous solution electrically produced from hypertonic salt solution as a disinfectant in these cases. In a series of fifty-nine which were bacteriologically positive, they were able to reduce the average time in hospital from 23.2 days in patients not treated to 16.4 days in those treated. Thacker[223] cocainizes the throat, then paints the parts with 50 per cent. silver nitrate. The nostrils are plugged with gauze soaked in 1 in 10 ichthyol in glycerin. Two applications cleared up eight diphtheria carriers. Ewart[224] suggests the instillation of jasmin oil into the nostrils as a means of ridding carriers of the organisms.

Lynch[225] believes in the efficacy of vaccines, but thinks tonsillectomy the ideal procedure. Love[226] treated seven persistent carriers with vaccines of killed diphtheria bacilli, without much apparent effect.

Several other observers unite in advocating the removal of tonsils and adenoids to clear up persistent carriers. Wherry[227] recommends

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219. McKay: Am. Jour. Pub. Health, 1915, **5,** 982.
220. Ott and Roy: Jour. Am. Med. Assn., 1916, **66,** 800.
221. Labbe and Canat: Paris méd., 1917, **7,** 9.
222. Beattie, Lewis and Gee: Brit. Med. Jour., 1917, **1,** 256.
223. Thacker: Brit. Med. Jour., 1916, **1,** 374.
224. Ewart: Brit. Med. Jour., 1915, **2,** 854.
225. Lynch: New Orleans Med. and Surg. Jour., 1916, **68,** 782.
226. Love: New Orleans Med. and Surg. Jour., 1916, **68,** 778.
227. Wherry: Western Med. Rev., 1916, **21,** 15.

it. Friedberg[228] removed them without any general ill effects. Cowie[229] found the method to be the most efficient of any. Rabinoff[230] says that the results with various other methods were disappointing, with the exception of those obtained with fuller's earth in adults, removal of tonsils and adenoids being recommended when other methods fail. Ruh, Miller and Perkins[231] conclude that the period of isolation for carriers can be materially shortened by the removal of these structures and no adverse effects were ever experiencd.

Meader[232] asserts that pathologic changes in the epithelium might be observed long after clinical manifestations had disappeared, but that these foci are not apparent to the unaided eye. While removal of the tonsils was followed by a report of negative cultures, still there is no data to show that foci on a large part of the mucosa might not still be infected. In his experience immunization with diphtheria bacilli vaccines was not a fruitful field of endeavor, inasmuch as he had been unable to demonstrate any trace of antibodies for these organisms.

Brown[233] sectioned the tonsils from seven diphtheria carriers and demonstrated gram-positive, beaded bacilli in great numbers in six. The one case which showed no gram-positive bacilli continued to give positive cultures, so that it is reasonable to infer that in this case the bacteria were multiplying in some other place than the tonsils.

Schick Test.—More has been written on the Schick test than on any other one phase of diphtheria, the practical value of the reaction having been amply demonstrated by many observers.

Park and Zingher[234] emphasize the great reliability of the test. A negative reaction obtained after the age of 2 or 3 years indicates that the individual is protected, probably indefinitely, against the disease. The great majority of reactions are true reactions and indicate an absence of antitoxin in the blood. The test is of value in clearing up clinically doubtful diagnoses of diphtheria and by its use the unnecessary sensitization of about one-half of exposed individuals may be avoided.

Zingher[235] found it to help in the diagnosis of nasal diphtheria, and thinks that the results obtained in families seem to point to other causes in addition to bacterial infection with virulent diphtheria bacilli as determining factors in the production of natural antitoxin.

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228. Friedberg: Jour. Am. Med. Assn., 1916, **66,** 810.
229. Cowie: Jour. Mich. Med. Soc., 1917, **16,** 72.
230. Rabinoff: Jour. Am. Med. Assn., 1916, **67,** 1722.
231. Ruh, Miller and Perkins: Jour. Am. Med. Assn., 1916, **66,** 941.
232. Meader: Med. Rec., New York, 1915, **88,** 127.
233. Brown: Jour. Infect. Dis., 1916, **19,** 565.
234. Park and Zingher: Am. Jour. Pub. Health, 1916, **6,** 431.
235. Zingher: Am. Jour. Obst., 1915, **72,** 735.

In a later communication Zingher[236] says that the accuracy of the results obtained with the test will depend not only on the toxin, but also on the care with which the test is made and on the interpretation of the reaction. A positive reaction should be considered as indicating a lack of immunity, unless the pseudoreaction can be eliminated by a control test. The results with the test obtained in 2,700 normal children show that from 17 to 32 per cent. between the ages of 2 and 16 years give a positive reaction and are probably susceptible to diphtheria.

Somewhat later the same worker[237] found the test to be positive between 1 and 4 years of age in about 32 per cent. of normal children, in a slightly larger proportion of cases of measles, in twice as many scarlet fever cases and nearly three times as many cases of poliomyelitis. He believes that susceptibility to one of the less communicable diseases, like poliomyelitis, indicates that the child is more apt to be susceptible to other infectious diseases. The presence or absence of natural immunity, as shown by the Schick test, could be profitably studied in its relation to the mendelian law.

Weaver and Rappaport[238] tested 194 healthy young adults with the Schick reaction, and of these 52.6 per cent. gave negative results. They believe that it seems reasonable to assume that mild and unrecognized attacks of diphtheria are responsible for the increasing proportion of persons immune to diphtheria with increasing age. They found the test to be of value in the diagnosis of carriers who are sick from other anginas than diphtheria, Weaver[174] showing that all carriers gave negative reactions. In scarlet fever 33.3 per cent. gave positive results. These workers find that a limited antitoxin production is probably to be expected in some instances after the reaction.

Kolmer[239] advocates delaying the reading of the toxin reaction until forty-eight hours have elapsed in order to allow slight false reactions to disappear, although in the presence of an outbreak it is best to regard all reactions of erythema and edema measuring a quarter of an inch or more in diameter as positive. As a practical procedure the test has two main applications: to detect those susceptible to diphtheria, and as an aid in the diagnosis of the disease.

Moffett and Conrad[240] studied the test in 455 children up to 14 years of age, concluding that it is of value in differentiating doubtful membranes in the throat; that it tests the efficacy of antitoxin immunization; that in institutional epidemics it is of value in lessening the

236. Zingher: Am. Jour. Dis. Child., 1916, **11,** 269.
237. Zingher: Am. Jour. Dis. Child., 1917, **13,** 247.
238. Weaver and Rappaport: Jour. Am. Med. Assn., 1916, **66,** 1448.
239. Kolmer: Penn. Med. Jour., 1916, **19,** 333.
240. Moffett and Conrad: Jour. Am. Med. Assn., 1915, **65,** 1011.

amount of antitoxin used by differentiating the susceptibles from the nonsusceptibles.

Greenebaum and Hettler,[241] Sewall,[242] Stovall,[243] Linenthal and Rubin,[244] Veeder,[245] Levinson,[246] Schiller,[247] Earle,[248] Sprenger[249] and others,[250] are agreed on the value of the test in differentiating doubtful membranes and as a prompt, economic and satisfactory method of controlling epidemics of diphtheria by a determination of susceptibility. Schiller thinks susceptibility is a family characteristic, but Sprenger disagrees. The latter found that carriers gave a negative reaction.

Earle thinks the test is unsatisfactory in the colored race, but Wright[251] states that the reaction is as clear cut in negroes as it is in whites. Bullen[252] retested 100 children after eleven months and found that 18 per cent. of those who gave a positive reaction in May, 1914, showed no reaction in April, 1915, while fifteen who gave no reaction when first tested showed more or less strongly marked reactions at the time of the second test.

In one series of sixty normal children Levinson and Blatt[253] found 78.13 per cent. were negative to the toxin test. In a series of fifty-five afflicted with diseases other than diphtheria or tuberculosis, 61.8 per cent. were negative. Of thirty-three children suspected of having tuberculosis, the Schick test seemed to have no effect on a simultaneous von Pirquet reaction, or vice versa. In thirty-eight tuberculous children, sixteen were positive, but the results bore no relation to the reaction obtained from tuberculin treatment.

Shaw and Youland[254] found that 47 per cent. of sixty-six children under 1 year of age and 58.6 per cent. of twenty-nine children in their second year gave positive reactions. They recommend that when virulent diphtheria bacilli are found in infants who have no antitoxin in their tissue, a careful examination for diphtheritic rhinitis should be made, as they had five cases in which it was overlooked clinically.

Cowie[255] found that successive intradermal injections of very dilute

241. Greenebaum and Hettler: Lancet-Clinic, 1916, **116,** 389.
242. Sewell: Jour. Mich. Med. Soc., 1916, **15,** 290.
243. Stovall: Jour. Am. Med. Assn., 1916, **66,** 804.
244. Linenthal and Rubin: Boston Med. and Surg. Jour., 1915, **173,** 427.
245. Veeder: Internat. Clin., 1916, **3,** 180.
246. Levinson: Illinois Med. Jour., 1915, **28,** 40.
247. Schiller: Wisconsin Med. Jour., 1916, **14,** 453.
248. Earle: Western Med. Rev., 1916, **21,** 24.
249. Sprenger: Illinois Med. Jour., 1916, **29,** 447.
250. Bullen: Am. Jour. Obst., 1915, **72,** 735.
251. Wright: Jour. Infect. Dis., 1917, **21,** 265.
252. Bullen: New York State Jour. Med., 1916, **16,** 208.
253. Levinson and Blatt: Arch. Diagnosis, 1915, **8,** 201.
254. Shaw and Youland: Am. Jour. Obst., 1916, **74,** 558.
255. Cowie: Am. Jour. Dis. Child., 1916, **12,** 266.

solutions of diphtheria toxin (0.00001 c.c. L+ dose), given at intervals varying from five to twelve days, provoke the formation of antibodies, and in those already exhibiting a certain degree of immunity, brings about a definite immunity as recognized by the intradermal test. The degree of immunity, however, cannot be compared with the results obtained by the use of toxin-antitoxin mixtures. An early primary reaction of ordinary degree indicates absence or low degree of immunity. A late appearing primary reaction indicates a greater degree of immunity than an early reaction. The development of immunity induced by small successive doses of toxin may be recognized by a hastening in the time of appearance of the reaction and a diminution in the size of the lesion. A primary reacting case which does not change its character after repeated injections may be considered to be without protecting bodies.

Hitchens and Tingley[256] found that the Schick test made intrapalpebrally was, to a considerable degree, anticipative of the antitoxin productiveness of horses.

Technic of the Test.—Koplik and Unger[257] believed that if the toxin injected approximated one-fiftieth the maximum lethal dose rather than accurately equaled that amount, all the indications of the test would be met. They, therefore, devised a needle so constructed that when it is inserted its full length, after being dipped into undiluted toxin, the amount of the latter carried in approximated one-fiftieth the maximum lethal dose.

Weaver and Rappaport[238] slightly modified the technic of the test, thrusting the needle into the skin at right angles to the surface to a depth of one-eighth inch. The direction is then changed so that if carried forward the needle would emerge one-half inch from the point of entrance. This method is less painful, requires less time than the old and obviates the escape of fluid.

Litterer[258] calls attention to the readiness with which diphtheria toxin deteriorates even in its native state. It must be of definite strength, else the test would be fallacious. He has made an effort to preserve a toxin so that it can be rendered stable for a reasonable period when subjected to room temperature. The most practicable method consisted in introducing dried toxin into a vial with 2 c.c. of sterile liquid albolene or toluol and immersing the whole in cold water. This rendered the toxin quite stable for six weeks at room temperature or for more than eight months at 48 F.

256. Hitchens and Tingley: Jour. Immunol., 1917, **2,** 395.
257. Koplik and Unger: Jour. Am. Med. Assn., 1916, **66,** 1195.
258. Litterer: Southern Med. Jour., 1917, **10,** 103.

To overcome the difficulties in popularizing the test, Zingher[259] presents a simplified outfit for the distribution of the toxin.[260] In working with the test, Perkins, Miller and Ruh[215] come to the conclusion, in agreement with other observers, that smaller amounts of fluid should be injected, that a small needle should be used, and that freshly sterilized salt solution gives a smaller proportion of false reactions than when old salt solution is used.

Pseudoreaction.—Zingher[261] says that the pseudoreaction of the toxin test is caused by the protein substance of the diphtheria bacillus which is present in the solution used for the test, and may be seen in those who have enough natural antitoxin to render them immune to diphtheria. Park[262] found that about 3 per cent. of cases tested gave a positive reaction. Levinson[246] says that no test should be considered positive unless there is induration measuring at least 0.5 by 0.2 cm., and a reaction persisting at least five days.

Kolmer and Moshage[263] made a study of the pseudoreaction and conclude that it is advisable, when doing Schick tests, to use as highly potent toxin as possible in order to dilute the protein constituents of the bouillon. The toxin should be so diluted that only 0.05 or 0.1 c.c. need be given, and not more than 0.25 per cent. of tricresol should be present. It is also better to read the reaction after forty-eight hours than after twenty-four hours. The use of bouillon controls aids in detecting these pseudoreactions.

Experimenting with the Schick reaction, Bessau and Schwenke[264] found an element in the bouillon which was not neutralizable by antitoxin and was apparently not modified by heat. They believe that in all probability this heat-resisting substance is a preformed toxin (endotoxin) in the diphtheria bacillus. The reaction to this endotoxin cannot be regarded as an index to the antitoxic content of the blood and hence of the immunity to diphtheria. It seems possible that the question of immunity to diphtheria, which seems to have been settled, may have to be studied anew.

Kolmer and Moshage[265] injected intracutaneously a polyvalent antigen of washed, neutralized and heat-killed diphtheria bacilli, which they call diphtherin, and observed an allergic skin reaction following in about 70 per cent. of children and 35 per cent. of adults. This reaction has no value as an index of immunity and is of practical inter-

259. Zingher: Med. Rec., New York, 1916, **84,** 667.
260. Zingher: Jour. Am. Med. Assn., 1916, **65,** 329.
261. Zingher: Jour. Am. Med. Assn., 1916, **66,** 1617.
262. Park: Med. Rec., New York., 1915, **88,** 505.
263. Kolmer and Moshage: Jour. Am. Med. Assn., 1915, **65,** 144.
264. Bessau and Schwenke: Monatschr. f. Kinderh., 1915, **13,** 397.
265. Kolmer and Moshage: Am. Jour. Dis. Child., 1916, **12,** 316.

est mainly from the point of view that it may be mistaken for a positive Schick reaction. Kolmer[266] further says that hypersensitiveness to diphtheria protein cannot be taken as an index to diphtheria immunity and that anaphylactic states bear no constant relation to the presence or absence of such antibodies as may be detected by experiments in vitro.

Toxin-Antitoxin Mixtures.—Park and Zingher[267] have done considerable work with toxin-antitoxin immunization. They find that individuals who, before treatment, gave a negative Schick reaction are probably immune for life and therefore it is not necessary to inject them, when exposed, with either antitoxin or toxin-antitoxin. If a longer protection is desired, those who are not immune may be given both antitoxin and toxin-antitoxin. For general prophylaxis in schools and communities, excluding immediate contacts, a mixture of toxin-antitoxin alone (from 85 to 90 per cent. of the L+ dose of toxin to each unit of antitoxin) or toxin-antitoxin plus a vaccine of killed diphtheria bacilli is recommended. The dose is 1 c.c. of toxin-antitoxin and 1,000,000,000 bacteria injected subcutaneously and repeated three times at intervals of six or seven days. Sufficient time has not elapsed to judge of the value of the addition of diphtheria bacilli. The early and late results of active immunization may be determined with the Schick test. In another communication they[268] say that while toxin-antitoxin injections cannot be depended on to prevent diphtheria in the presence of immediate danger of infection, because of the slow development of immunity in the majority of cases, yet the injection is of value in rendering a community or school population immune from the danger of future infection up to a period of possibly several years.

Later in the year they[269] presented statistics based on over 1,000 cases that had been actively immunized. No harmful after-effects were noted. The retest with the Schick reaction showed that only 30 to 40 per cent. became immune within three weeks after the first injection, about 50 per cent. by the fourth week, 70 to 80 per cent. by the sixth week, and 90 to 95 per cent. by the eighth to twelfth week. In a group studied over a period of one and one half years, it was found that immunity persisted at least that time. From their results Park and Zingher conclude that it is advisable to immunize children soon after the first year of life in order to confer protection against diphtheria at a time when the disease is most dangerous. An immune child population could thus be developed with the result that fresh clinical cases

266. Kolmer: Jour. Immunol., 1916, **67,** 1333.
267. Park and Zingher: Jour. Am. Med. Assn., 1915, **65,** 2216.
268. Park and Zingher: Proc. New York Path. Soc., 1915, **15,** 110.
269. Park and Zingher: Med. Rec., New York, 1916, **90,** 741.

would be prevented and the bacillus carrier would probably soon disappear as a hygienic factor in the community.

Park[270] noticed that those who have natural antitoxin respond rapidly to the injection of toxin-antitoxin mixtures, but in those without antitoxin no appreciable response occurs for fourteen days, and in 50 per cent. not for four weeks. The full response is not seen until the third month. Only 95 per cent. of susceptibles become immune. Park believes the procedure has its most practical value in institutions.

Bullen[250] injected forty-one children having positive Schick tests with toxin-antitoxin mixtures. When tested later, all but eight still had markedly positive reactions.

Lynch[225] urges that children be immunized by the von Behring method before they are admitted to the public schools, unless the Schick test is negative.

Busson and Lowenstein[271] tried the effects of toxin-antitoxin mixtures on animals. In using mixtures that were kept in the icebox for one or two months, a change occurred that permitted doubly neutralized mixtures to produce the same immunity as exactly neutralized or underneutralized mixtures. They obtained no better results by reinjection of the mixture.

Opitz[272] declares that even one antitoxic unit per cubic centimeter of serum does not protect against diphtheria, therefore in active immunization one should strive for as high an antitoxic content as possible. Excretion of passively introduced antibodies occurs independently of the day of the disease, of the gravity of the disease, and of the size of the dose of serum, occurring more or less rapidly in the weeks following injection.

Linenthal and Rubin[244] gave thirty-six children 750 units of antitoxin each. This produced an immunity which lasted not over four weeks in half the children, eight weeks in several, and in six children it persisted after five months.

Cultural Diagnosis.—Walthall[273] showed that the pharynx may be negative for Klebs-Loeffler bacilli, but that they may be present in the nose or larynx, and that one tonsil may give positive cultures while all other portions of the mucous membrane are negative. Geiger, Kelly and Bathgate[274] lay stress on the importance of nose cultures. In a series of cultures those from the nose gave 42.2 per cent. positive and from the throat 7.9 per cent. positive.

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270. Park: Boston Med. and Surg. Jour., 1916, **175,** 721.
271. Busson and Lowenstein: Ztschr. f. exper. Path. u. Therap., 1915, **17,** 289.
272. Opitz: Deutsch. med. Wchnschr., 1915, **41,** 914.
273. Walthall: Am. Jour. Dis. Child., 1916, **12,** 149.
274. Geiger, Kelly and Bathgate: Jour. Am. Med. Assn., 1916, **66,** 645.

Clark's[275] statistics from various countries emphasize the vital importance of commencing treatment at the earliest possible moment, early diagnosis being the important factor. Seidel[276] says that a twenty-hour culture should not be regarded as sufficient for a negative diagnosis, but a forty-four-hour culture should be examined. Neff[277] urges that direct smears be taken from patients with a membrane in order to hasten the diagnosis. Then it is not necessary to wait for the result of a culture. He[278] believes the mortality is much too high, and urges that an earlier diagnosis be made or that antitoxin be administered without waiting for cultural confirmation.

Morbidity and Mortality.—Crum[163] conservatively estimates that not fewer than 250,000 lives are at present saved annually from the ravages of diphtheria through the use of antitoxin and other improved methods of diagnosis and treatment. The disease, however, still causes more deaths than whooping cough, measles or scarlet fever, the annual number of deaths being 17,000.

Baginsky[279] reports on 525 cases of diphtheria in one year with a mortality of 15.6 per cent. with the use of antitoxin, in contrast with a mortality of 48.21 per cent. in the year before serum was used. Of those treated on the first day the mortality was 1.07 per cent., on the sixth day, 19.2 per cent. and on the seventh day, 27.2 per cent. The death rate in the Alexandra Hospital, according to Cushing and Murphy,[280] was 7.5 per cent. over a period of ten years. Of 205 patients intubated or tracheotomized, fifty-five died, a rate of 27 per cent., but in 1915 only 16 per cent. of intubated patients died. The mortality is always raised by the septic cases in which the patients first improve, then die of cardiac failure, and by hemorrhagic cases, twelve of which occurred in the above mentioned series, and in which all patients died.

Reiche[281] contrasts the diphtheria incidence and mortality of four communities, two of which were prosperous and two very much lower in the social scale. The percentage of mortality in the prosperous communities was 4.13 as against 15.8 in the other.

The death rate from diphtheria and croup in 1915 in the registration area[282] was 10,544, or 15.7 per 100,000, having fallen from 43.3 in 1900. This decline of more than 60 per cent. is relatively greater than that shown by any other important cause of death except typhoid fever.

275. Clark: Brazil-méd., 1916, **30,** 417.
276. Seidel: München. med. Wchnschr., 1915, **62,** 1209.
277. Neff: Jour. Am. Med. Assn., 1915, **65,** 585.
278. Neff: Jour. Kansas Med. Soc., 1916, **16,** 142.
279. Baginsky: Berl. klin. Wchnschr., 1915, **52,** 1268.
280. Cushing and Murphy: Canada Med. Assn. Jour., 1916, **6,** 817.
281. Reiche: Berl. klin. Wchnschr., 1915, **52,** 643.
282. Jour. Am. Med. Assn., 1916, **67,** 1457.

Hitchcock[283] investigated seventy-three deaths from diphtheria in the Connecticut Valley and found that the physician's first visit was not made until the fourth day or later in 53.5 per cent. of the cases, while 36.9 per cent. of patients died on or before the fifth day. He believes that any case which is clinically suspicious enough to warrant taking a culture for diagnostic purposes is suspicious enough to warrant the administration of antitoxin without waiting to hear from the culture.

Prophylactic Serum Treatment.—Cushing and Murphy[280] found the danger of infection to attendants greater from diphtheria than from any other disease treated in the hospital. No attempt was ever made to immunize the attendants with prophylactic injections of serum, as it was felt that the benefits of the resulting brief immunity were not in proportion to the discomfort and disability of the serum reaction. Better quarters and better care of the attendants has apparently materially decreased the number of secondary cases among them.

Weaver and Rappaport[238] give every nurse in the Durand Hospital who shows a positive Schick reaction, 1,000 units of antitoxin. Every month they are retested and are reimmunized when a positive reaction again appears.

In reply to a questionnaire sent to Spanish physicians by Alvarez,[284] inquiring as to their experience with antitoxin, they were unanimous in asserting that the fear of by-effects should not prevent its use for curative purposes. Its administration as a preventive occasioned considerable difference of opinion, the majority agreeing, however, that its use in hospitals, asylums, etc., is justified when the disease is epidemic.

Antitoxin Dosage and Methods of Administration.—Bell[285] believes it strange that after the lapse of twenty-six years since the discovery of antitoxin it should be necessary to herald its virtues or urge its use. While there are few physicians who do not use it at all, there are many who do not use it properly. He urges the use of sufficiently large doses and much prefers the intramuscular and intravenous methods of administration. There is no limit to the dose, so far as danger is concerned, the only thing to fear is that it may be too small. Practically, Bell finds that the intravenous method is very simple, one of the veins at the bend of the elbow being preferred and an ordinary antitoxin syringe used. Woody[277] advocates very large doses, the average given by him being 23,800 units. He feels, however, that the advantage of the intravenous method of administration are overbalanced by the difficulties of its use, particularly in general practice and in children, and he favors the intramuscular route as having many advantages over the subcutaneous method.

283. Hitchcock: Boston Med. and Surg. Jour., 1916, **175,** 718.
284. Alvarez: Siglo méd., 1916, **63,** 630.
285. Bell: Ohio State Med. Jour., 1916, **12,** 618.

Others (see Footnotes 277, 286, 287, 288, 289) urge that large doses be given at the first injection, Stammel[286] advising that croup cases which do not clear up within two or three hours be treated as diphtheria, and that antitoxin be administered without waiting for the result of cultures. Many (see Footnotes 290, 291, 292, 287, 280) are strongly in favor of the intravenous method, especially in the laryngeal form of the disease. Ferguson[287] says that he has not seen a patient die who has lived twenty-four hours after antitoxin was given. Dupaquier[292] believes that when the technic of the intravenous method is perfected it will be the routine manner of giving antitoxin. Lynah,[187] on the other hand, prefers the intramuscular route.

Antitoxin Standardization. — MacConkey[293] examined thirty-one samples of antitoxin which had been in commerce for an average period of two and a half years, and found that it showed an average loss of 23 per cent. or about 10 per cent. a year. The author concludes that unless one knows how the serum has been stored, the time expiration label means nothing and may lead to a false sense of security.

The Committee on Standard Methods of Preparing Diphtheria Antitoxin[294] supplement their report of four years ago, giving in detail Banzhof's latest method of refining and concentrating serum.

Heinemann[295] succeeded by a combination of well-known methods and persistent repetition of certain details in producing a serum with a higher concentration than obtained with former methods. Because nontoxic proteins are eliminated the solids of the new preparation need not be higher than 18 to 20 per cent. This serum is of attractive appearance, water clear for at least one year and its consistence is such that it is easily discharged through a hypodermic syringe. The antitoxic globulins realized by this method are easily soluble and dialysis is consequently rapid. Nonantitoxic protein being eliminated in large measure, serum disease, so far as present observations go, is greatly reduced.

Treatment of Laryngeal Diphtheria.—Bell[296] reports the use of a tube for thirty-one days. This was an apparently hopelessly sick 1-year-old baby, which completely recovered. The very distressing

286. Stammel: Lancet-Clinic, 1915, **113,** 655.
287. Ferguson: Illinois Med. Jour., 1915, **28,** 401.
288. Delearde: Bull. de l'Acad. de méd., Paris, 1916, **76,** 173.
289. Capitan: Bull. de l'Acad. de méd., Paris, 1916, **75,** 653.
290. Bell: Lancet-Clinic, 1915, **114,** 104.
291. Greene: South. Med. Jour., 1917, **10,** 164.
292. Dupaquier: New Orleans Med. and Surg. Jour., 1915, **68,** 145.
293. MacConkey: Brit. Med. Jour., 1917, **1,** 10.
294. Heinemann, Anderson, Park, Hitchens and Pease: Am. Jour. Pub. Health, 1916, **6,** 751.
295. Heinemann: Jour. Infect. Dis., 1916, **19,** 433.
296. Bell: Arch. Pediat., 1916, **33,** 161.

cough was relieved by dropping 2 per cent. cocain solution into the tracheal tube at intervals. A tracheotomy had had to be performed also.

Local Methods of Treatment.—Local treatment of diphtheria with tribrombetanaphthol has the advantage, according to Leshke,[297] of causing the membrane to disappear sooner, of favorably affecting the clinical course, and of rapidly developing freedom from bacilli, thus preventing the spread of infection.

Treatment of Post-Diphtheritic Paralysis.—Passler[298] noted rapid improvement of a postdiphtheritic paralysis and eventual recovery within a month, under large doses of antitoxin. Maggiore[299] treated a boy suffering from postdiphtheritic paralysis with injections of a vaccine made with an emulsion of inactivated diphtheria bacilli in diphtheria antitoxin. The paralysis began to improve at once. Maggiore regards the factors involved as those on which active immunity is based.

Weaver and Rappaport[238] tested three cases of postdiphtheritic paralysis with the Schick test. In one the reaction was positive. After administration of antitoxin the advancing paralysis stopped abruptly and recovery rapidly followed.

Serum Sickness.—With a view to ascertaining the frequency and severity of the symptoms of serum sickness, Sturtevant[300] studied 500 consecutive cases receiving serum. He found that of 422 patients receiving one injection, 20 per cent. showed symptoms. The larger the amount of serum, the larger the number reacting. Most reactions occurred from the fifth to the ninth day, though they occurred as early as the first and as late as the seventeenth day. The symptoms were a rash, nausea and vomiting, albuminuria and edema occasionally, either alone or together, and joint symptoms in about 14 per cent. of reacting cases.

Cushing and Murphy[280] have no record of true anaphylactic shock and death in the Alexandria Hospital, though serum is given both intramuscularly and intravenously. They are convinced that the latter method has a distinct future.

Hassler[301] reports the death of an apparently well child twenty minutes after the subcutaneous injection of 1,000 units of antitoxin. The postmortem diagnosis and probable cause of death was status lymphaticus.

Netter[302] states that grave accidents following subcutaneous injections of diphtheria serum are rare.

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297. Leshke: München, med. Wchnschr., 1915, **62,** 1381.
298. Passler: München. med. Wchnschr., 1916, **63,** 92.
299. Maggiore: Pediatria, 1917, **25,** 193.
300. Sturtevant: Arch. Int. Med., 1916, **17,** 176.
301. Hassler: California State Med. Jour., 1917, **15,** 153.
302. Netter: Arch. de méd. d enf., 1916, **19,** 505.

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